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(71) Applicant *(for all designated States except US)*: **ARENA PHARMACEUTICALS, INC.** [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TEEGARDEN, Bradley** [US/US]; 11933 Windom Peak Way, San Diego, CA 92131 (US). **DROUET, Keith** [US/US]; 10751 Juniper Park Lane, San Diego, CA 92121 (US). **JAYAKUMAR, Honnappa** [US/US]; 13323 Caminito Ciera, #107, San Diego, CA 92129 (US). **THOMSEN, William** [US/US]; 13603 Mar Scenic, Del Mar, CA 92014 (US). **MAFFUID, Paul** [US/US]; 3326 Avenida Anacapa, Carlsbad, CA 92009 (US). **ELWELL, Katie** [US/US]; 103 Guerrero Court, Solana Beach, CA 92075 (US). **FOSTER, Richard** [GB/GB]; Puffins Cottage, Poundstock Bude, Cornwall EX23 0AX (GB). **LAWLESS, Michael** [US/US]; 1847 Willow Oak Drive, St. Charles, MO 63303 (US). **LIU, Qian** [US/US]; 310 Shady Meadows Drive, Ballwin, MO 63011 (US). **SMITH, Julian** [GB/GB]; 2 Exeview Cottages, Whitestone, Exeter, Devon EX4 2JJ (GB). **FEICHTINGER, Konrad** [DE/US]; 3533 6th Avenue, #3, San Diego, CA 92103 (US).

(74) Agents: **BRADFUTE, David** et al.; Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Drive, San Diego, CA 92121 (US).

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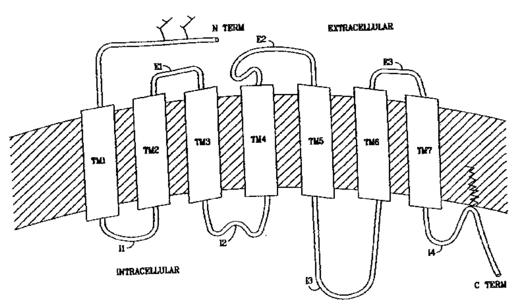
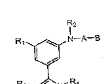
[Continued on next page]

(54) Title: SMALL MOLECULE MODULATORS OF THE 5-HT2A SEROTONIN RECEPTOR USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO





(I)

(57) Abstract: The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Formula (I): Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggreagation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D2 receptor antagonist such as haloperidol, administered separately or together.

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SMALL MOLECULE MODULATORS OF THE 5-HT2A SEROTONIN RECEPTOR USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO

FIELD OF THE INVENTION

The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggreagation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders.

The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D2 receptor antagonist such as haloperidol, administered separately or together.

BACKGROUND OF THE INVENTION

I. G protein-coupled receptors

[0001] G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, Gq, Gs, Gi and Go are G proteins that have been identified. The general structure of G protein-coupled receptors is shown in Figure 1.

[0002] Under physiological conditions, G protein-coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. As shown schematically in Figure 2, a receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

[0003] A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

Serotonin receptors

[0004] Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to on anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.,* lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

[0005] Serotonin receptors are divided into seven subfamilies, referred to as 5-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The human 5-HT_{2C} receptor was first isolated and cloned in 1987, and the human 5-HT_{2A} receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT_{2A} and 5-HT_{2C} receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

[0006] U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT1C receptor (now known as the 5-HT_{2C} receptor). U.S. Patent Number 5,661,012 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{2A} receptor.

[0007] Mutations of the endogenous forms of the rat 5-HT_{2A} and rat 5-HT_{2C} receptors have been reported to lead to constitutive activation of these receptors (5-HT_{2A}: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, hereinafter "Casey"; 5-HT_{2C}: Herrick-Davis, K., and Teitler, M. (1996*) Society for Neuroscience Abstracts*, 22:699.18, hereinafter "Herrick-Davis 1"; *and* Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT_{2A} receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position 312 of the rat 5-HT_{2C} receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

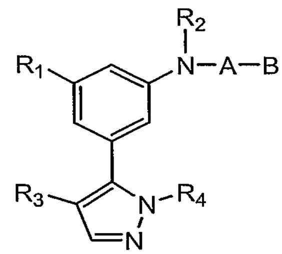
SUMMARY OF THE INVENTION

[0008] The present invention relates to non-endogenous, constitutively activated forms of the human 5-HT_{2A} and human 5-HT_{2C} receptors and various uses of such receptors. Further disclosed are small molecule modulators of these receptors. Most preferably, these modulators have inverse agonist characteristics at the receptor.

[0009] More specifically, the present invention discloses nucleic acid molecules and the proteins for three non-endogenous, constitutively activated human serotonin receptors, referred to herein as, AP-1, AP-3, and AP-4. The AP-1 receptor is a constitutively active form of the human 5-HT_{2C} receptor created by an S310K point mutation. The AP-3 receptor is a constitutively active form of the human 5-HT2A receptor whereby the intracellular loop 3 (IC3) portion and the cytoplasmic-tail portion of the endogenous human 5-HT2A receptor have been replaced with the IC3 portion and the cytoplasmic-tail portion of the human 5-HT_{2C} receptor. The AP-4 receptor is a constitutively active form of the human 5-HT2A receptor whereby (1) the region of the intracellular third loop between the proline of the transmembrane 5 region (TM5) and the proline of TM6 of the endogenous human 5-HT_{2A} receptor has been replaced with the corresponding region of the human 5-HT_{2C} receptor (including a S310K point mutation); and (2) the cytoplasmic-tail portion of the endogenous human 5-HT_{2A} receptor has been replaced with the cytoplasmic-tail portion of the endogenous human 5-HT_{2C} receptor.

[0010] The invention also provides assays that may be used to directly identify candidate compounds as agonists, partial agonists or inverse agonists to non-endogenous, constitutively activated human serotonin receptors; such candidate compounds can then be utilized in pharmaceutical composition(s) for treatment of diseases and disorders which are related to the human 5-HT_{2A} and/or human 5-HT_{2C} receptors.

[0011] The invention also provides compounds that exhibit high selectivity 5-HT_{2A} activity. More specifically, the compounds possessing 5-HT_{2A} receptor activity are designated by the general Formula (I):



(I)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

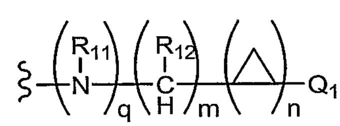
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



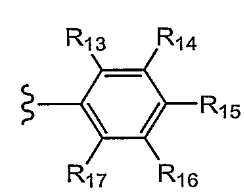
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of

said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt.

[0012] These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] In the following figures, bold typeface indicates the location of the mutation in the non-endogenous, constitutively activated receptor relative to the corresponding endogenous receptor.

[0014] **Figure 1** shows a generalized structure of a G protein-coupled receptor with the numbers assigned to the transmembrane helices, the intracellular loops, and the extracellular loops.

[0015] **Figure 2** schematically shows the active and inactive states for a typical G protein-coupled receptor and the linkage of the active state to the second messenger transduction pathway.

[0016] **Figure 3a** provides the nucleic acid sequence of the endogenous human 5-HT_{2A} receptor (**SEQ.ID.NO.:22**).

[0017] **Figure 3b** provides the corresponding amino acid sequence of the endogenous human 5-HT2A receptor (**SEQ.ID.NO.:23**).

[0018] **Figure 4a** provides the nucleic acid sequence of the endogenous human 5-HT_{2C} receptor (**SEQ.ID.NO.:24**).

[0019] **Figure 4b** provides the corresponding amino acid sequence of the endogenous human 5-HT_{2C} receptor (**SEQ.ID.NO.:25**).

[0020] **Figure 5a** provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2C} receptor ("AP-1 cDNA" - **SEQ.ID.NO.:26**).

[0021] **Figure 5b** provides the corresponding amino acid sequence of the AP-1 cDNA ("AP-1" - **SEQ.ID.NO.:27**).

[0022] **Figure 6a** provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2A} receptor whereby the IC3 portion and the cytoplasmic-tail portion of the endogenous 5-HT_{2A} receptor have been replaced with the IC3 portion and the cytoplasmic-tail portion of the human 5-HT_{2C} receptor ("AP-3 cDNA" - **SEQ.ID.NO.:28**).

[0023] **Figure 6b** provides the corresponding amino acid sequence of the AP-3 cDNA ("AP-3" - **SEQ.ID.NO.:29**).

[0024] **Figure 6c** provides a schematic representation of AP-3, where the dashed-lines represent the portion obtained from the human 5-HT_{2C} receptor.

[0025] **Figure 7a** provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2A} receptor whereby (1) the region of the between the proline of TM5 and the proline of TM6 of the endogenous human 5-HT_{2A} receptor has been replaced with the corresponding region of the human 5-HT_{2C} receptor (including a S310K point mutation); and (2) the cytoplasmic-tail portion of the endogenous 5-HT_{2A} receptor has been replaced with the cytoplasmic-tail portion of the endogenous human 5-HT_{2C} receptor ("AP-4 cDNA" - **SEQ.ID.NO.:30**).

[0026] **Figure 7b** provides the corresponding amino acid sequence of the AP-4 cDNA ("AP-4" - **SEQ.ID.NO.:31**).

[0027] **Figure 7c** provides a schematic representation of the mutated 5-HT_{2A} receptor of Figure 7b where the dashed-lines represent the portion obtained from the human 5-HT_{2C} receptor.

[0028] **Figure 8** is a representation of the preferred vector, pCMV, used herein.

[0029] **Figure 9** is a diagram illustrating (1) enhanced (^{35}S)GTPγS binding to membranes prepared from COS cells expressing the endogenous human 5-HT_{2C} receptor in response to serotonin, and (2) inhibition by mianserin using wheatgerm agglutinin scintillation proximity beads. The concentration of (^{35}S)GTPγS was held constant at 0.3 nM, and the concentration of GDP was held at 1 μM. The concentration of the membrane protein was 12.5 μg.

[0030] **Figure 10** is a diagram showing serotonin stimulation of (^{35}S)GTPγS binding to membranes expressing AP-1 receptors in 293T cells and the inhibition by 30 μM mianserin on Wallac™ scintistrips.

[0031] **Figures 11A and 11B** are diagrams showing the effects of protein concentration on (^{35}S)GTPγS binding in membranes prepared from 293T cells transfected with the endogenous human 5-HT_{2C} receptors and AP-1 receptors compared to cells transfected with the control vector (pCMV) alone in the absence (**Figure 11A**) and presence (**Figure 11B**) of 10 μM serotonin. The radiolableled concentration of (^{35}S)GTPγS was held constant at 0.3 nM, and the GDP concentration was held constant at 1 μM. The assay was performed on 96-well format on Wallac™ scintistrips.

[0032] **Figure 12** provides bar-graph comparisons of inositol tris-phosphate ("IP3") production between the endogenous human 5-HT_{2A} receptor and AP-2, a mutated form of the receptor.

[0033] **Figure 13** provides bar-graph comparisons of inositol tris-phosphate ("IP3") production between the endogenous human 5-HT2A receptor and AP-4, a mutated form of the receptor.

[0034] **Figure 14** provides bar graph comparisons of IP3 production between the endogenous human 5-HT2A receptor and AP-3, a mutated form of the receptor.

[0035] **Figure 15** provides bar-graph comparisons of IP3 production between the endogenous human 5-HT_{2C} receptor and AP-1.

[0036] **Figures 16A-C** provides representative autoradiograms showing displacement of I^{125}-LSD from brain sections by spiperone and Compound 1.

[0037] **Figures 17A-C** show *in vivo* response of animals to Compound 2 exposure.

DEFINITIONS

[0038] The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control.

[0039] AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

[0040] AMINO ACID ABBREVIATIONS used herein are set out in TABLE 1:

TABLE 1

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

[0041] PARTIAL AGONISTS shall mean moieties which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

[0042] ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

[0043] CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) which is amenable to a screening technique.

[0044] COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.

[0045] COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.

[0046] CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to constitutive receptor activation.

[0047] CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.

[0048] CONTACT or CONTACTING shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

[0049] ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor" shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus.

[0050] In contrast, the term NON-ENDOGENOUS in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For

example, and not a limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

[0051] INHIBIT or INHIBITING, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

[0052] INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

[0053] LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

[0054] As used herein, the terms MODULATE or MODULATING shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule. For example, Compounds which modulate/capable of modulating the 5-HT_{2A} activity include agonists, inverse agonists, antagonists, inhibitors, activators, and compounds which directly or indirectly affect regulation of the 5-HT_{2A} activity.

[0055] PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

[0056] STIMULATE or STIMULATING, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

DETAILED DESCRIPTION

[0057] In addition to the foregoing beneficial uses for the modulators of 5-HT_{2A} receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

USE OF THE COMPOUNDS OF THE INVENTION

1. Antiplatelet Therapies (5-HT_{2A} mediated platelet aggregation):

[0058] Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

[0059] In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

[0060] A transient ischemic attack ("TIA" or "mini-stroke") is a brief imterruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

[0061] Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

[0062] Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation blood clots that cause first or second strokes.

[0063] Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

[0064] Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

[0065] Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

[0066] 5-HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy. See Satimura, K, et al., Clin Cardiol 2002 Jan. 25 (1):28-32; and Wilson, H.C et al., Thromb Haemost 1991 Sep 2;66(3):355-60.

[0067] The 5-HT_{2A} inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limitation, the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of said treatment, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

[0068] In further embodiments, the present invention provides methods for reducing risk of blood clot formation in a angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to a said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

2. Asthma

[0069] It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in the pathophysiology of acute asthma. See Cazzola, M. and Matera, M.G., TIPS, 2000, 21, 13; and De

Bie, J.J. et al., British J. Pharm., 1998, 124, 857-864. The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of said treatment, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of said treatment, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

3. Agitation

[0070] Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721).

[0071] Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 11(suppl 2):S45-S50).

[0072] An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia. Of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

[0073] Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia

[0074] Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al., Arch Gen Psychiatry 2000 Oct., 57(10):968-976).

[0075] The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimers disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including with out limitation stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

4. Add-on therapy to Haloperidol in the treatment of schizophrenia and other disorders:

[0076] Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (*See*, American Statistical and Diagnostic Handbook).

[0077] Haloperidol (Haldol) is a potent dopamine D2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5-HT_{2A} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

[0078] Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5-HT_{2A} inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

[0079] In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

[0080] In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to said patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

[0081] In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

[0082] In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

[0083] In further embodiments, the present invention provides methods for treating schizophrenia in a patient in need of said treatment comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D2 receptor antagonist is haloperidol.

[0084] The administration of the dopamine D2 receptor antagonist can be concomitant with administration of the 5-HT_{2A} inverse agonist, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious

reduction or elimination of deleterions haloperidol effects. In some embodiments, haloperidol and the 5-HT_{2A} inverse agonist are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

[0085] The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from said schizophrenia, comprising administering to said patient a 5-HT_{2A} inverse agonist as disclosed herein.

PARTICULARLY PREFERRED MUTATIONS

[0086] For convenience, the sequence information regarding the non-endogenous, constitutively active human 5-HT_{2A} and 5-HT_{2C} receptors are referred to by identifiers as set forth in TABLE 2:

TABLE 2

IDENTIFIER	RECEPTOR	SEQ.ID.NO.:	FIGURE
AP-1 cDNA	5-HT_{2C}	28	5a
AP-1	5-HT_{2C}	29	5b
AP-3 cDNA	5-HT_{2A}	30	6a
AP-3	5-HT_{2A}	31	6b
AP-4 cDNA	5-HT_{2A}	32	7a
AP-4	5-HT_{2A}	33	7b

As will be discussed in greater detail below, a mutation analogous to that reported by Casey (C322K) was utilized in the human 5-HT_{2A} receptor and is referred to herein as AP-2. However, AP-2 did not lead to sufficient constitutive activation to allow for utilization in screening techniques.

INTRODUCTION

[0087] While it is sometimes possible to make predictions as to the effect of nucleic acid manipulation from one species to another, this is not always the case. The results reported by Casey suggest that a point mutation in the rat 5-HT_{2A} receptor evidences constitutive activation of the mutated receptor. Casey reports that the C322K mutation was approximately four fold more active than the native rat 5-HT_{2A} receptor. However, for purposes of a most preferred use, i.e., screening of candidate compounds, this corresponding mutation in the human 5-HT_{2A} receptor had little

discernable effect in evidencing constitutive activation of the human receptor. This, of course, creates the reasonable conclusion that the information reported in Herrick-Davis 1 or Herrick-Davis 2 is of limited predictive value relative to the manipulation of the human 5-HT_{2C} receptor. Consequently, the ability to make reasonable predictions about the effects of mutations to the rat 5-HT receptors vis-à-vis the corresponding human receptors is not possible. Nonetheless, this unfortunate lack of reasonable predictability provides the opportunity for others to discover mutations to the human 5-HT receptors that provide evidence of constitutive activation.

[0088] Therefore, the present invention is based upon the desire of defining mutated sequences of the human serotonin receptors 5-HT_{2A} and 5-HT_{2C} whereby such mutated versions of the expressed receptor are constitutively active. These constitutively active receptors allow for, inter alia, screening candidate compounds.

[0089] What has been discovered and disclosed herein is that substantial activation of the human 5-HT_{2A} receptor can be obtained by "domain swapping," i.e., by switching the third intracellular domain of the 5-HT_{2A} receptor with the third intracellular domain of the 5-HT_{2C} receptor. Additionally, swapping the cytoplasmic tail of the two receptors further increases the IP3 response. Furthermore, mutation of the serine at position 310 to lysine (S31OK) of the human 5-HT_{2C} receptor leads to constitutive activation.

[0090] What follows is a most preferred approach to identification of candidate compounds; those in the art will readily appreciate that the particular order of screening approaches, and/or whether or not to utilize certain of these approaches, is a matter of choice. Thus, the order presented below, set for presentational efficiency and for indication of the most preferred approach utilized in screening candidate compounds, is not intended, nor is to be construed, as a limitation on the disclosure, or any claims to follow.

GENERIC G PROTEIN-COUPLED RECEPTOR SCREENING ASSAY TECHNIQUES

[0091] When a G protein receptor becomes constitutively active, it binds to a G protein (Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, (^{35}S)GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that (^{35}S)GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among

other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor. .

CONFIRMATION OF G PROTEIN-COUPLED RECEPTOR SITE SCREENING ASSAY TECHNIQUES

[0092] Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.* an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain. Thus, by further screening those candidate compounds, which have been identified using a "generic" assay in an agonist and/or antagonist competitive binding assay, further refinement in the selection process is provided.

[0093] Lysergic acid diethylamide (LSD) is a well-known agonist of the 5-HT_{2A} and 5-HT_{2C} receptors, while mesulergine is a well-known antagonist to the 5-HT_{2C} receptor. Accordingly, in most preferred embodiments, an agonist (LSD) and/or antagonist (mesulergine) competitive binding assay(s) is used to further screen those compounds selected from the "generic" assay for confirmation of serotonin receptor binding.

SPECIFIED G PROTEIN ASSAY TECHNIQUES

[0094] The art-accepted physiologically mediated pathway for the human 5-HT_{2A} and 5-HT_{2C} receptors is via Gq. Intracellular accumulation of IP3 can be used to confirm constitutive activation of these types of Gq coupled receptors (see Herrick-Davis-1). As a result, "IP3 accumulation" assays can be used to further screen those compounds selected from an agonist and/or antagonist competitive binding assay. .

PHARMACEUTICAL COMPOSITIONS

[0095] Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-

acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

EXAMPLES

[0096] The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. It is intended that equivalent, non-endogenous, constitutively activated human serotonin receptor sequences include those having eighty-five percent (85%) homology, more preferably having ninety percent (90%) homology, and most preferably having ninety-five percent (95%) homology to the disclosed and claimed sequences all fall within the scope of any claims appended hereto.

EXAMPLE 1

GENERATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN SEROTONIN RECEPTORS 5-HT$_{2C}$ AND 5-HT$_{2A}$

A. Construction of constitutively active 5-HT$_{2C}$ receptor cDNA

1. Endogenous Human 5-HT$_{2C}$

[0097] The cDNA encoding endogenous human 5-HT$_{2C}$ receptor was obtained from human brain poly-A$^+$ RNA by RT-PCR. The 5' and 3' primers were derived from the 5' and 3' untranslated regions and contained the following sequences: .

5'-GACCTCGAGGTTGCTTAAGACTGAAGCA-3' (**SEQ.ID.NO.:1**)

5'-ATTTCTAGACATATGTAGCTTGTACCGT-3' (**SEQ.ID.NO.:2**)

PCR was performed using either TaqPlus™ precision polymerase (Stratagene) or rTth™ polymerase (Perkin Elmer) with the buffer systems provided by the manufacturers, 0.25 μM of each primer, and 0.2 mM of each of the four (4) nucleotides. The cycle condition was 30 cycles of 94°C for 1 minute, 57 °C for 1 minute and 72 °C for 2 minutes. The 1.5 kb PCR fragment was digested with Xho I and Xba I and subcloned into the Sal I-Xba I site of pBluescript.

[0098] The derived cDNA clones were fully sequenced and found to correspond to published sequences.

2. AP-1 cDNA

[0099] The cDNA containing a S310K mutation (AP-1 cDNA) in the third intracellular loop of the human 5-HT_{2C} receptor was constructed by replacing the Sty I restriction fragment containing amino acid 310 with synthetic double stranded oligonucleotides encoding the desired mutation. The sense strand sequence utilized had the following sequence:

5'-CTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTAAGAAAGTC-3' **(SEQ.ID.NO.:3)**

and the antisense strand sequence utilized had the following sequence:

5'-CAAGGACTTTCTTAGCTTTTCTTTCATTGTTGATAGCCTGCATGGTGCCC-3' **(SEQ.ID.NO.:4)**.

B. Construction of constitutively active 5-HT_{2A} receptor cDNA

1. Endogenous Human 5-HT_{2A}

[0100] The cDNA encoding endogenous human 5-HT_{2A} receptor was obtained by RT-PCR using human brain poly-A^+ RNA; a 5' primer from the 5' untranslated region with a Xho I restriction site:

5'-GACCTCGAGTCCTTCTACACCTCATC-3' (SEQ.ID.NO.:5)

and a 3' primer from the 3' untranslated region containing an Xba I site:

5'-TGCTCTAGATTCCAGATAGGTGAAAA CTTG-3' **(SEQ.ID.NO.:6)**.

PCR was performed using either TaqPlus™ precision polymerase (Stratagene) or rTth™ polymerase (Perkin Elmer) with the buffer systems provided by the manufacturers, 0.25 μM of each primer, and 0.2 mM of each of the four (4) nucleotides. The cycle condition was 30 cycles of 94°C for 1 minute, 57 °C for 1 minute, and 72 °C for 2 minutes. The 1.5 kb PCR fragment was digested with Xba I and subcloned into the Eco RV-Xba I site of pBluescript.

[0101] The resulting cDNA clones were fully sequenced and found to encode two amino acid changes from the published sequences. The first change is a T25N mutation in the N-terminal extracellular domain and the second change is an H452Y mutation. These mutations are likely to represent sequence polymorphisms rather than PCR errors since the cDNA clones having the same two mutations were derived from two independent PCR procedures using Taq polymerase from two different commercial sources (TaqPlus™ Stratagene and rTth™ Perkin Elmer).

2. Human 5-HT_{2A} (C322K; AP-2)

[0102] The cDNA containing the point mutation C322K in the third intracellular loop was constructed by using the Sph I restriction enzyme site, which encompasses amino acid 322. For the PCR procedure, a primer containing the C322K mutation:

5'-CAAAGAAAGTACTGGGCATCGTCTTCTTCCT-3' (SEQ.ID.NO.:7)

was used along with the primer from the 3' untranslated region set forth above as **SEQ.ID.NO.:6.** The resulting PCR fragment was then used to replace the 3' end of the wild type 5-HT_{2A} cDNA by the T4 polymerase blunted Sph I site. PCR was performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer and 10% DMSO, 0.25 mM of each primer, 0.5mM of each of the 4 nucleotides. The cycle conditions were 25 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute.

3. AP-3 cDNA

[0103] The human 5-HT_{2A} cDNA with intracellular loop 3 (IC3) or IC3 and cytoplasmic tail replaced by the corresponding human 5-HT_{2C} cDNA was constructed using PCR-based mutagenesis.

(a) Replacement of IC3 Loop

[0104] The IC3 loop of human 5-HT_{2A} cDNA was first replaced with the corresponding human 5-HT_{2C} cDNA. Two separate PCR procedures were performed to generate the two fragments, Fragment A and Fragment B, that fuse the 5-HT_{2C} IC3 loop to the transmembrane 6 (TM6) of 5-HT_{2A}. The 237 bp PCR fragment, Fragment A, containing 5-HT_{2C} IC3 and the initial 13 bp of 5-HT_{2A} TM6 was amplified by using the following primers:

5'-CCGCTCGAGTACTGCGCCGACAAGCTTTGAT-3' **(SEQ.ID.NO.:8)**

5'-CGATGCCCAGCACTTTCGAAGCTTTTCTTTCATTGTTG-3'**(SEQ.ID.NO.:9)**

The template used was human 5-HT_{2C} cDNA.

[0105] The 529 bp PCR fragment, Fragment B, containing the C-terminal 13 bp of IC3 from 5-HT_{2C} and the C-terminal of 5-HT_{2A} starting at beginning of TM6, was amplified by using the following primers:

5'-AAAAGCTTCGAAAGTGCTGGGCATCGTCTTCTTCCT-3' **(SEQ.ID.NO.:10)**

5'-TGCTCTAGATTCCAGATAGGTGAAAACTTG-3' **(SEQ.ID.NO.:11)**

The template used was human 5-HT_{2A} cDNA.

[0106] Second round PCR was performed using Fragment A and Fragment B as co-templates with **SEQ.ID.NO.:8** and **SEQ.ID.NO.:11** (it is noted that the sequences for **SEQ.ID.NOS.:6** and **11** are the same) as primers. The resulting 740 bp PCR fragment, Fragment C, contained the IC3 loop of human 5-HT_{2C} fused to TM6 through the end of the cytoplasmic tail of human 5-HT_{2A}. PCR was performed using pfu™ polymerase (Stratagene) with the buffer system provided by the manufacturer, and 10% DMSO, 0.25 mM of each primer, and 0.5 mM of each of the four (4) nucleotides. The cycle conditions were 25 cycles of 94 °C for 1 minute, 57 °C (1st round PCR) or 60 °C (2nd round PCR) for 1 minute, and 72 °C for 1 minute (1st round PCR) or 90 seconds (2nd round PCR).

[0107] To generate a PCR fragment containing a fusion junction between the human 5-HT_{2A} TM5 and the IC3 loop of 5-HT_{2C}, four (4) primers were used. The two external primers, derived from human 5-HT_{2A}, had the following sequences:
5'-CGTGTCTCTCCTTACTTCA-3' (**SEQ.ID.NO.:12**)

[0108] The other primer used was **SEQ.ID.NO.:6** (*see* note above regarding **SEQ.ID.NOS.:6** and **11**). The first internal primer utilized was an antisense strand containing the initial 13 bp of IC3 of 5-HT_{2C} followed by the terminal 23 bp derived from TM5 of 5-HT_{2A}:
5'-TCGGCGCAGTACTTTGATAGTTAGAAAGTAGGTGAT-3' (**SEQ.ID.NO.:13**)

[0109] The second internal primer was a sense strand containing the terminal 14 bp derived from TM5 of 5-HT_{2A} followed by the initial 24 bp derived from IC3 of 5-HT_{2C}:
5'-TTCTAACTATCAAAGTACTGCGCCGACAAGCTTTGATG-3' (**SEQ.ID.NO.:14**).

[0110] PCR was performed using endogenous human 5-HT_{2A} and a co-template, Fragment C, in a 50 ml reaction volume containing 1X pfu buffer, 10% DMSO, 0.5 mM of each of the four (4) nucleotides, 0.25 mM of each external primer (**SEQ.ID.NOS.:11** and **12**), 0.06 mM of each internal primer (**SEQ.ID.NOS.:13** and **14**) and 1.9 units of pfu polymerase (Stratagene). The cycle conditions were 25 cycles of 94°C for 1 minute, 52°C for 1 minute, and 72 °C for 2 minutes and 10 seconds. The 1.3 kb PCR product was then gel purified and digested with Pst I and Eco RI. The resulting 1 kb PstI-Eco RI fragment was used to replace the corresponding fragment in the endogenous human 5-HT_{2A} sequence to generate the mutant 5-HT_{2A} sequence encoding the IC3 loop of 5-HT_{2C}.

(b) Replacement of the cytoplasmic tail

[0111] To replace the cytoplasmic tail of 5-HT_{2A} with that of 5-HT_{2C}, PCR was performed using a sense primer containing the C-terminal 22 bp of TM7 of endogenous human 5-HT_{2A} followed by the initial 21 bp of the cytoplasmic tail of endogenous human 5-HT_{2C}:
5'-TTCAGCAGTCAACCCACTAGTCTATACTCTGTTCAACAAAATT-3' (**SEQ.ID.NO.:15**)
The antisense primer was derived from the 3' untranslated region of endogenous human 5-HT_{2C}:
5'-ATTTCTAGACATATGTAGCTTGTACCGT-3' (**SEQ.ID.NO.:16**).

[0112] The resulting PCR fragment, Fragment D, contained the last 22 bp of endogenous human 5-HT_{2A} TM7 fused to the cytoplasmic tail of endogenous human 5-HT_{2C}. Second round PCR was performed using Fragment D and the co-template was endogenous human 5-HT_{2A} that was previously digested with Acc I to avoid undesired amplification. The antisense primer used was **SEQ.ID.NO.:16** (the sequences for **SEQ.ID.NOS.:16** and **2** are the same) and the sense primer used was derived from endogenous human 5-HT_{2A}:

5'-ATCACCTACTTTCTAACTA-3' (**SEQ.ID.NO.:17**).

[0113] PCR conditions were as set forth in Example 1B3(a) for the first round PCR, except that the annealing temperature was 48 °C and the extension time was 90 seconds. The resulting 710 bp PCR product was digested with Apa I and Xba I and used to replace the corresponding Apa I-Xba I fragment of either (a) endogenous human 5-HT_{2A}, or (b) 5-HT_{2A} with 2C IC3 to generate (a) endogenous human 5-HT_{2A} with endogenous human 5-HT_{2C} cytoplasmic tail and (b) AP-3, respectively.

4. **AP-4 cDNA**

[0114] This mutant was created by replacement of the region of endogenous human 5-HT_{2A} from amino acid 247, the middle of TM5 right after Pro^{246}, to amino acid 337, the middle of TM6 just before Pro^{338}, by the corresponding region of AP-1 cDNA. For convenience, the junction in TM5 is referred to as the "2A-2C junction," and the junction in TM6 is referred to as the "2C-2A junction."

[0115] Three PCR fragments containing the desired hybrid junctions were generated. The 5' fragment of 561 bp containing the 2A-2C junction in TM5 was generated by PCR using endogenous human 5-HT_{2A} as template, **SEQ.ID.NO.:12** as the sense primer, and the antisense primer was derived from 13 bp of 5-HT_{2C} followed by 20 bp of 5-HT_{2A} sequence:

5'-CCATAATCGTCAGGGGAATGAAAAATGACACAA-3' (**SEQ.ID.NO.:18**)

[0116] The middle fragment of the 323 bp contains endogenous human 5-HT_{2C} sequence derived from the middle of TM5 to the middle of TM6, flanked by 13 bp of 5-HT_{2A} sequences from the 2A-2C junction and the 2C-2A junction. This middle fragment was generated by using AP-1 cDNA as a template, a sense primer containing 13 bp of 5-HT2A followed by 20 bp of 5-HT_{2C} sequences across the 2A-2C junction and having the sequence:

5'-ATTTTTCATTCCCCTGACGATTATGGTGATTAC-3' (**SEQ.ID.NO.:19**);

and an antisense primer containing 13 bp of 5-HT_{2A} followed by 20 bp of 5-HT_{2C} sequences across the 2C-2A junction and having the sequence:

5'-TGATGAAGAAAGGGCACCACATGATCAGAAACA-3' (**SEQ.ID.NO.:20**).

The 3' fragment of 487 bp containing the 2C-2A junction was generated by PCR using endogenous human 5-HT_{2A} as a template and a sense primer having the following sequence from the 2C-2A junction:

5'-GATCATGTGGTGCCCTTTCTTCATCACAAACAT-3' (**SEQ.ID.NO.:21**)

and the antisense primer was **SEQ.ID.NO.:6** (*see* note above regarding **SEQ.ID.NOS.:6** and **11**).

[0117] Two second round PCR reactions were performed separately to link the 5' and middle fragment (5'M PCR) and the middle and 3' fragment (M3' PCR). The 5'M PCR co-template used

was the 5' and middle PCR fragment as described above, the sense primer was **SEQ.ID.NO.:12** and the antisense primer was **SEQ.ID.NO.:20**. The 5'M PCR procedure resulted in an 857 bp PCR fragment.

[0118] The M3' PCR used the middle and M3' PCR fragment described above as the co-template, **SEQ.ID.NO.:19** as the sense primer and **SEQ.ID.NO.:6** (see note above regarding **SEQ.ID.NOS.:6** and **11**) as the antisense primer, and generated a 784 bp amplification product. The final round of PCR was performed using the 857 bp and 784 bp fragments from the second round PCR as the co-template, and **SEQ.ID.NO.:12** and **SEQ.ID.NO.:6** (see note above regarding **SEQ.ID.NOS.:6** and **11**) as the sense and the antisense primer, respectively. The 1.32 kb amplification product from the final round of PCR was digested with Pst I and Eco RI. Then resulting 1 kb Pst I-Eco RI fragment was used to replace the corresponding fragment of the endogenous human 5-HT_{2A} to generate mutant 5-HT_{2A} with 5-HT_{2C}: C310K/IC3. The Apa I-Xba fragment of AP3 was used to replace the corresponding fragment in mutant 5-HT_{2A} with 5-HT_{2C}: C310K/IC3 to generate AP4.

EXAMPLE 2

RECEPTOR EXPRESSION

A. pCMV

[0119] Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous receptors discussed herein, it is most preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351. *See* Figure 8.

B. Transfection procedure

[0120] For the generic assay ((^{35}S)GTPγS; Example 3) and the antagonist binding assay (mesulergine; Example 4), transfection of COS-7 or 293T cells was accomplished using the following protocol.

[0121] On day one, $5x10^6$ COS-7 cells or $1x10^7$ 293T cells per 150mm plate were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 μg DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.2 ml

serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120 μl lipofectamine (Gibco BRL) in 1.2 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45 min. The admixture is referred to as the "transfection mixture". Plated COS-7 cells were washed with 1X PBS, followed by addition of 10 ml serum free DMEM. 2.4 ml of the transfection mixture was then added to the cells, followed by incubation for 4 hrs at 37°C/5% CO_2. The transfection mixture was then removed by aspiration, followed by the addition of 25 ml of DMEM/10% Fetal Bovine Serum. Cells were then incubated at 37°C/5% CO_2. After 72 hr incubation, cells were then harvested and utilized for analysis.

EXAMPLE 3

GTP MEMBRANE BINDING SCINTILLATION PROXIMITY ASSAY

[0122] The advantages of using (^{35}S)GTPγS binding to measure constitutive activation are that: (a) (^{35}S)GTPγS binding is generically applicable to all G protein-coupled receptors; and (b) (^{35}S)GTPγS binding is proximal at the membrane surface, thereby making it less likely to pick-up molecules which affect the intracellular cascade. The assay utilizes the ability of G protein-coupled receptors to stimulate (^{35}S)GTPγS binding to membranes expressing the relevant receptors. Therefore, the assay may be used to directly screen compounds at the disclosed serotonin receptors.

[0123] Figure 9 demonstrates the utility of a scintillation proximity assay to monitor the binding of (^{35}S)GTPγS to membranes expressing, *e.g.*, the endogenous human 5-HT_{2C} receptor expressed in COS cells. In brief, a preferred protocol for the assay is such that the assay was incubated in 20 mM HEPES, pH 7.4, binding buffer with 0.3 nM (^{35}S)GTPγS and 12.5 μg membrane protein and 1 μM GDP for 30 minutes. Wheatgerm agglutinin beads (25 μl; Amersham) were then added and the mixture was incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter. As shown in FIG. 9, serotonin, which as the endogenous ligand activates the 5-HT_{2C} receptor, stimulated (^{35}S)GTPγS binding to the membranes in a concentration dependant manner. The stimulated binding was completely inhibited by 30 μM mianserin, a compound considered as a classical 5-HT_{2C} antagonist, but also known as a 5-HT_{2C} inverse agonist.

[0124] Although this assay measures agonist-induced binding of (^{35}S)GTPγS to membranes and can be routinely used to measure constitutive activity of receptors, the present cost of wheatgerm agglutinin beads may be prohibitive. A less costly but equally applicable alternative also meets the needs of large-scale screening. Flash plates and Wallac™ scintistrips may be used to format a high throughput (^{35}S)GTPγS binding assay. This technique allows one to monitor the tritiated ligand

binding to the receptor while simultaneously monitoring the efficacy via (^{35}S)GTPγS binding. This is possible because the Wallac™ beta counter can switch energy windows to analyze both tritium and ^{35}S-labeled probes.

[0125] Also, this assay may be used for detecting of other types of membrane activation events that result in receptor activation. For example, the assay may be used to monitor ^{32}P phosphorylation of a variety of receptors (including G protein-coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound (^{35}S)GTPγS or the ^{32}P-phosphorylated receptor will activate the scintillant coated on the wells. Use of Scinti® strips (Wallac™) demonstrate this principle. Additionally, this assay may be used for measuring ligand binding to receptors using radiolabeled ligands. In a similar manner, the radiolabeled bound ligand is centrifuged to the bottom of the well and activates the scintillant. The (^{35}S)GTPγS assay results parallel the results obtained in traditional second messenger assays of receptors.

[0126] As shown in Figure 10, serotonin stimulates the binding of (^{35}S)GTPγS to the endogenous human 5-HT_{2C} receptor, while mianserin inhibits this response; furthermore, mianserin acts as a partial inverse agonist by inhibiting the basal constitutive binding of (^{35}S)GTPγS to membranes expressing the endogenous human 5-HT_{2C} receptor. As expected, there is no agonist response in the absence of GDP since there is no GDP present to exchange for (^{35}S)GTPγS. Not only does this assay system demonstrate the response of the native 5-HT_{2C} receptor, but it also measures the constitutive activation of other receptors.

[0127] Figure 11A and Figure 11B demonstrate the enhanced binding of (^{35}S)GTPγS to membranes prepared from 293T cells expressing the control vector alone, the native human 5-HT_{2C} receptor or the AP-1 receptor was observed (data not shown). The total protein concentration used in the assay affects the total amount of (^{35}S)GTPγS binding for each receptor. The c.p.m. differential between the CMV transfected and the constitutively active mutant receptor increased from approximately 1000 c.p.m at 10 μg/well to approximately 6-8000 c.p.m. at 75 μg/well protein concentration, as shown in Figure 11.

[0128] The AP-1 receptor showed the highest level of constitutive activation followed by the wild type receptor, which also showed enhanced (^{35}S)GTPγS binding above basal. This is consistent with the ability of the endogenous human 5-HT_{2C} receptor to accumulate intracellular IP3 in the absence of 5-HT stimulation (Example 5) and is also consistent with published data claiming that the endogenous human 5-HT_{2C} receptor has a high natural basal activity. Therefore, the AP-1 receptor

demonstrates that constitutive activity may be measured by proximal (^{35}S)GTPγS binding events at the membrane interface.

EXAMPLE 4

SEROTONIN RECEPTOR AGONIST/ANTAGONIST COMPETITIVE BINDING ASSAY

[0129] Membranes were prepared from transfected COS-7 cells (*see* Example 2) by homogenization in 20 mM HEPES and 10 mM EDTA, pH 7.4 and centrifuged at 49,000 x g for 15 min. The pellet was resuspended in 20 mM HEPES and 0.1 mM EDTA, pH 7.4, homogenized for 10 sec. using a Polytron homogenizer (Brinkman) at 5000 rpm and centrifuged at 49,000 x g for 15 min. The final pellet was resuspended in 20 mM HEPES and 10 mM $MgCl_2$, pH 7.4, homogenized for 10 sec. using polytron homogenizer (Brinkman) at 5000 rpm.

[0130] Assays were performed in triplicate 200 µl volumes in 96 well plates. Assay buffer (20 mM HEPES and 10 mM $MgCl_2$, pH 7.4) was used to dilute membranes, ^{3}H-LSD, ^{3}H-mesulergine, serotonin (used to define non-specific for LSD binding) and mianserin (used to define non-specific for mesulergine binding). Final assay concentrations consisted of 1 nM ^{3}H-LSD or 1 nM ^{3}H-mesulergine, 50 µg membrane protein and 100 µm serotonin or mianserin. LSD assays were incubated for 1 hr at 37° C, while mesulergine assays were incubated for 1 hr at room temperature. Assays were terminated by rapid filtration onto Wallac Filtermat Type B with ice cold binding buffer using Skatron cell harvester. The radioactivity was determined in a Wallac 1205 BetaPlate counter.

EXAMPLE 5

INTRACELLULAR IP_3 ACCUMULATION ASSAY

[0131] For the IP_3 accumulation assay, a transfection protocol different from the protocol set forth in Example 2 was utilized. In the following example, the protocols used for days 1-3 were slightly different for the data generated for Figures 12 and 14 and for Figures 13 and 15; the protocol for day 4 was the same for all conditions.

A. COS-7 and 293 Cells

[0132] On day one, COS-7 cells or 293 cells were plated onto 24 well plates, usually 1x10^5 cells/well or 2x10^5 cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 ug DNA (*see* Example 2) in 50 µl serum-free DMEM/well and then 2 µl lipofectamine in 50 µl serum-free DMEM/well. The solutions ("transfection media") were gently mixed and incubated for 15-30 minutes at room temperature. The cells were washed with 0.5 ml PBS and then 400 µl of serum free media was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37°C/5%CO_2. Then the transfection media was removed and replaced with

1ml/well of regular growth media. On day 3, the media was removed and the cells were washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum-free media (GIBCO BRL) was added to each well with 0.25 μCi of ^{3}H-myo-inositol/well and the cells were incubated for 16-18 hours overnight at 37°C/5% CO_2. Protocol A.

B. 293 Cells

[0133] On day one, 1x10^7 293 cells per 150 mm plate were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 μg DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.2 ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120 μl lipofectamine (Gibco BRL) in 1.2 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45 min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4 ml of the transfection mixture was then added to the cells, followed by incubation for 4 hrs at 37°C/5% CO_2. On day 3, cells were trypsinized and counted, followed by plating of 1x10^6 cells/well (poly D-lysine treated 12-well plates). Cells were permitted to adhere to the wells, followed by one wash with 1xPBS. Thereafter, 0.5 μCi ^{3}H-inositol in 1ml inositol-free DMEM was added per well. Protocol B.

[0134] On day 4, the cells were washed with 0.5 ml PBS and then 0.45 ml of assay medium was added containing inositol-free/serum free media, 10 μM pargyline, 10 mM lithium chloride, or 0.4 ml of assay medium and 50 μl of 10x ketanserin (ket) to a final concentration of 10 μM. The cells were then incubated for 30 minutes at 37° C. Then the cells were washed with 0.5 ml PBS and 200 μl of fresh/ice cold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) was added/well. The solution was kept on ice for 5-10 minutes or until the cells were lysed and then neutralized by 200 μl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate was then transferred into 1.5 ml micro-centrifuge tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 seconds and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100-200 mesh). The resin was washed with water and 0.9 ml of the upper phase was loaded onto the column. The column was washed with 10 ml of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol trisphosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H_2O and stored at room temperature in water. Results are discussed below.

[0135] Figure 12 is an illustration of IP3 production from the human 5-HT_{2A} receptor which was mutated using the same point mutation as set forth in Casey, which rendered the rat receptor constitutively active. The results represented in Figure 12, support the position that when the point mutation shown to activate the rat receptor is introduced into the human receptor, little activation of the receptor is obtained that would allow for appropriate screening of candidate compounds, with the response being only moderately above that of the endogenous human 5-HT_{2A} receptor. Generally, a response of at least 2X above that of the endogenous response is preferred.

[0136] Figure 13 provides an illustration comparing IP3 production from endogenous 5-HT_{2A} receptor and the AP4 mutation. The results illustrated in Figure 13 support the position that when the novel mutation disclosed herein is utilized, a robust response of constitutive IP3 accumulation is obtained (e.g., over 2X that of the endogenous receptor).

[0137] Figure 14 provides an illustration of IP3 production from AP3. The results illustrated in Figure 14 support the position that when the novel mutation disclosed herein is utilized, a robust response of constitutive IP3 accumulation is obtained.

[0138] Figure 15 provides bar-graph comparisons of IP3 accumulation between endogenous human 5-HT_{2C} receptor and AP-1. Note that the endogenous receptor has a high degree of natural constitutive activity relative to the control CMV transfected cells (i.e., the endogenous receptor appears to be constitutively activated).

Example 6

Screening of Compounds Known to Have 5-HT_{2C} Antagonist Activity Against Non-Endogenous, Constitutively Activated Human Serotonin Receptor: AP-1

[0139] A final concentration of 12.5 μg membranes prepared from COS7 cells (see Example 2) transiently expressing constitutively active mutant human 5-HT_{2C} receptor AP-1 were incubated with binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM $MgC1_2$° 6H,O, 0.2% saponin, and 0.2 mM ascobate), GDP(1 μM) and compound in a 96-well plate format for a period of 60 minutes at ambient room temperature. Plates were then centrifuged at 4,000 rpm for 15 minutes followed by aspiration of the reaction mixture and counting for 1 minute in a Wallac™ MicroBeta plate scintillation counter. A series of compounds known to possess reported 5-HT_{2C} antagonist activity were determined to be active in the (^{35}S)GTPγS binding assay using AP-1. IC_{50} determinations were made for these commercially available compounds (RBI, Natick, Mass.). Results are summarized in **TABLE** 3. For each determination, eight concentrations of test compounds were tested in triplicate.

The negative control in these experiments consisted of AP-1 receptor without test compound addition, and the positive control consisted of 12.5 μg/well of COS7 cell membranes expressing the CMV promoter without expressed AP-1 receptor.

TABLE 3

Test Compound	Known Pharmacology	IC_{50} (nM) in GTP-γ-(^{35}S) Assay
Metergoline	5-HT2/lC antagonist	32.0
Mesulergine	5-HT2/lC antagonist	21.2
Methysergide	5-HT2/lC antagonist	6.1
Methiothepin	5-HTl antagonist	20.4
Normethylclozapin	5-HT2/lC antagonist	21.4
Fluoxetine	5-HT reuptake inhibitor	114.0
Ritanserin	5-HT2/lC antagonist	19.4

The IC_{50} results confirm that the seven tested compounds showed antagonist activity at the AP-1 receptor.

EXAMPLE 7

SCREENING OF CANDIDATE COMPOUNDS AGAINST NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN SEROTONIN RECEPTORS: AP-1

[0140] Approximately 5,500 candidate compounds (Tripos, Inc., St. Louis, MO) were screened using the assay protocol of Example 3 (with AP-1 mutant receptor) for identification as inverse agonists against the receptor; for this assay, an arbitrary cut-off of at least 50% inhibition was established for identification of inverse agonists. Approximately 120 of these compounds evidenced at least 50% inhibition of (^{35}S) GTPγS binding at 10 μM candidate compound (data not shown).

EXAMPLE 8

SCREENING OF SELECTED COMPOUNDS TO CONFIRM RECEPTOR BINDING: AP-1

[0141] The candidate compounds identified from Example 7 were then screened using the assay protocol of Example 4 (mesulergine), using the AP-1 mutant receptor. IC_{50} (nM) values were determined; five of the nearly 120 compounds of Example 7 were determined to have potent binding affinity for the receptor. Results are summarized in **TABLE** 4.

TABLE 4

Candidate Compound	IC_{50} (nM) in Mesulergine Assay
Compound **3**	205.0
Compound **4**	46.5
Compound **5**	209.0
Compound **6**	147.0
Compound **7**	1,810.0

EXAMPLE 9A

GENERAL SCREENING PARADIGM: SELECTION OF PRE-CLINICAL CANDIDATE LEADS

[0142] The "primary" screen designed to directly identify human $5\text{-HT}_{2A}/5\text{-HT}_{2C}$ receptor inverse agonists consisted of a membrane-based GTPγS binding assay utilizing membranes prepared from COS7 cells transiently transfected with AP-1 human receptor. Candidate compounds (10μM final assay concentration) directly identified as inhibiting receptor-mediated increases in GTPγS binding by greater than 50-75% (arbitrary cut-off value) were considered active "hits". Primary assay hits were then re-tested in the same assay to reconfirm their inverse agonist activity. If primary assay hits were reconfirmed active (50% or greater inhibition), and therefore directly identified as, *e.g.*, an inverse agonist, one of two approaches were available: (a) so-called "directed libraries" could be created, *i.e.*, additional candidate compounds were synthesized based upon the structures of the reconfirmed hits (geared towards, *e.g.*, improvement in the characteristics of the compounds) whereby the directed library compounds were then evaluated for the ability to compete for radioligand binding to both mutant 5-HT_{2C} (AP-1) and endogenous 5-HT_{2A} receptors, or (b) the reconfirmed hits were then evaluated for the ability to compete for radioligand binding to both mutant 5-HT_{2C} (AP-1) and endogenous 5-HT_{2A} receptors. Thus, when approach (a) was used, because these directed library candidate compounds were based upon the structures of compounds that were directly identified from the membrane-based GTPγS binding assay, the directed library compounds were not re-tested in the membrane-based GTPγS binding assay but rather were then confirmed via the radioligand binding analysis. The radioligand binding analysis tests were initially performed at 10μM test compound in triplicate and if the compound inhibited radiolabeled binding by 50% or more, the analysis was followed by eight concentration competition curves to determine Ki values. The last step in secondary assay evaluation was to determine if test compounds were capable of inhibiting AP-3 receptor-

mediated accumulation of inositol phosphates (*e.g.*, IP_3). This final assay confirms that the directly identified compounds retained inverse agonist properties.

Example 9B

CONSTITUTIVELY ACTIVATED HUMAN 5-HT_{2C} RECEPTOR (AP-1) MEDIATED FACILITATION OF GTPγS BINDING TO COS7 MEMBRANES

[0143] This protocol is substantially the same as set forth above in Example 6. Primary screening assays measuring GTPγS binding to membranes prepared from COS7 cells transiently transfected with human mutated 5-HT_{2C} receptor (AP-1) were used to directly identify inverse agonists in screening libraries (Tripos, Inc.). Candidate compound screens were performed in a total assay volume of 200 µl using scintillant-coated Wallac Scintistrip™ plates. The primary assay was comprised of the following chemicals (at indicated final assay concentrations): 20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM $MgCl_2$, 0.2% saponin, 0.2 mM ascorbic acid, 1 µM GDP, 0.3 nM $GTP\gamma^{35}S$, and 12.5 µg of the above defined membranes. Incubations were performed for 60 minutes at ambient room temperature. The binding assay incubation was terminated by centrifugation of assay plates at 4,000 rpm for 15 minutes, followed by rapid aspiration of the reaction mixture and counting in a Wallac MicroBeta™ scintillation counter.

[0144] Primary screening of candidate compounds initially involved testing of 72 test compounds per assay plate (96-well plates were utilized), at a final assay concentration of 10 µM candidate compound, in single replicates. A total of sixteen wells of each plate were dedicated for an eight concentration clozapine (a confirmed 5-$HT_{2C}/_{2A}$ inverse agonist) dose response curve (duplicate determinations at each concentration). Finally, a total of five assay wells of each plate were dedicated to define the negative control (AP-1 receptor expressing membranes without addition of candidate compounds) and three wells from each plate to define the positive control (membranes without AP-1 receptor) .

[0145] Reconfirmation experiments involve re-testing candidate compounds in the same assay described above, except that candidate compounds were evaluated in triplicate, thus allowing evaluation of 24 compounds per 96-well assay plate. Similar to the primary assay plates, an eight concentration clozapine dose response curve (duplicate determinations at each concentration) and the same negative and positive control wells were also included within each 96-well plate.

Example 9C(1)

COMPETITION STUDIES FOR DIRECTLY IDENTIFIED COMPOUNDS: MUTATED HUMAN 5-HT$_{2C}$ RECEPTOR (AP-1)

[0146] Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients consisted of assay buffer (20 mM HEPES and 10 mM $MgCl_2$), 1nM (^{3}H) mesulergine, and 50 µg of membranes (COS7 with AP-1 as defined above). Nonspecific (^{3}H) mesulergine binding was defined in the presence of 100 µM mianserin. Incubations were performed for 1 hour at 37°C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (each containing 100 µM mianserin). For one concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM, in triplicate. For IC_{50} determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated, in triplicate. A total of 16 wells were designated for an eight concentration mianserin dose response curve evaluation for both assays.

EXAMPLE 9C(2)

COMPETITION STUDIES WILD TYPE HUMAN 5-HT$_{2A}$ RECEPTOR

[0147] Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients comprised assay buffer (20 mM HEPES and 10mM $MgCl_2$), 1nM (^{3}H)LSD, and 50 µg of the above-defined membranes (COS7 with AP-1). Nonspecific (^{3}H)LSD binding was defined in the presence of 100 µM serotonin. Incubations were performed for 1 hour at 37° C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (containing 100 µM mianserin). For one concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM in triplicate. For IC_{50} determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated in triplicate. A total of 16 wells were designated for an eight concentration serotonin dose response curve evaluation for both assays.

EXAMPLE 9D

RECEPTOR-MEDIATED INOSITOL PHOSPHATE ACCUMULATION

[0148] Candidate compound identified in the assays of Examples 9A-9C were then evaluated for inositol phosphate accumulation, following the protocol of Example 5 (COS7 cells expressing human mutated 5-HT_{2A} receptor, AP-3), modified as follows: tube A was prepared by mixing 16 µg DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.0 ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 60 µl lipofectamine (Gibco BRL) in 1.0 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30 min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 10 ml Serum Free DMEM, followed by addition of 11 ml Serum Free DMEM. 2.0 ml of the transfection mixture was then added to the cells, followed by incubation for 5 hrs at 37° C/5% CO_2. On day 3, cells were trypsinized and counted, followed by plating of $1x10^6$ cells/well (12-well plates). Cells were permitted to adhere to the wells for 8 hrs, followed by one wash with 1xPBS. Thereafter, 0.5 µCi ^{3}H-inositol in 1ml inositol-free DMEM was added per well.

[0149] On day 4, the cells were washed with 1.5 ml PBS and then 0.9 ml of assay medium was added containing inositol-free/serum free media, 10 µM pargyline, 10 mM lithium chloride, for 5min in 37°C/5% CO_2 followed by 100µl addition of candidate compound diluted in the same material. The cells were then incubated for 120 minutes at 37° C. Then the cells were washed with 1.5 ml PBS and 200 µl of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) was added/well. The solution was kept on ice for 5-10 minutes or until the cells were lysed and then neutralized by 200 µl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate was then transferred into 1.5 ml micro-centrifuge tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 seconds and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100-200 mesh). The resin was washed with water and 0.9 ml of the upper phase was loaded onto the column. The column was washed with 10 ml of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol trisphosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with ddH_2O and stored at room temperature in water.

[0150] Following this round of assaying, candidate compounds having an IC_{50} value of less than 10 µM were considered as potential leads for the development of pharmaceutical compositions.

SCREENING CANDIDATE COMPOUNDS

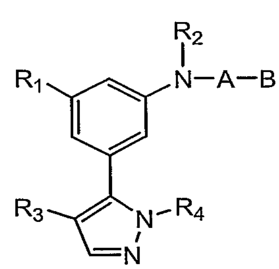
[0151] Following the protocols set forth above, one compound, Compound 7 (Example 8, *supra*) evidenced the following results as shown in TABLE 4A:

TABLE 4A

Compd No.	GTPγS AP-1 Percent Inhibition Relative To Positive Control (Primary)	GTPγS AP-1 Percent Inhibition Relative To Positive Control (Reconfirm)	Competitive Binding AP-1 ((^{3}H)mesulergine) IC_{50} Value (nM)	Competitive Binding WT 5-HT_{2A} ((^{3}H)LSD) IC_{50} Value (nM)	Inositol Phosphate Accumulation AP-3 IC_{50} Value (nM)
7	-1%	31%	2100 850	46	52 90

[0152] Based upon these results, structure activity analysis of the Compound 7 compound suggested that a series of derivatives of 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine would exhibit similar 5-HT_{2A} activity and selectivity. A series of derivatives of 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine were synthesized. These "directed" library compounds (Tripos, Inc.) were then analyzed in accordance with the protocols of Examples 9c(1), 9c(2) and 9d.

[0153] This series of compounds exhibits highly selective 5-HT_{2A} activity. Accordingly, in one aspect of the invention, a series of compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors is designated by the general Formula (I):



(I)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2,

OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen,

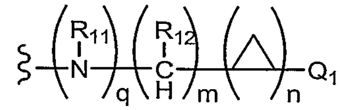
$-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



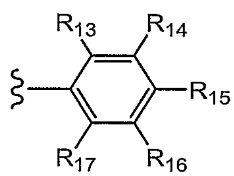
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt.

[0154] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle. C_{1-6} alkyl moieties can be straight chain or branched; optionally substituted C_{1-6}

alkyl moieties can be straight chain or branched; C_{2-6} alkenyl moieties can be straight chain or branched; and optionally substituted C_{2-6} alkenyl moieties can be straight chain or branched. Examples of suitable C_{1-6} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl. Halogens are typically F, Cl, Br, and I. Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalinyl, quinazolinyl and benzothienyl.

[0155] In some embodiments of the foregoing Formula (I), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0156] In some embodiments of the foregoing Formula (I), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0157] In some embodiments of the compounds of Formula (I), B is L_1, q is 1, m is 0, and n is 0. In further embodiments of the compounds of Formula (I), B is L_1, q is 1, m is 1, and n is 0. In further embodiments of the compounds of Formula (I), B is L_1, q is 1, m is 0, and n is 1. In further embodiments of the compounds of Formula (I), B is L_1, q is 0, m is 0, and n is 0.

[0158] In some embodiments of the compounds of Formula (I), B is L_2. In further embodiments of the compounds of Formula (I), A, is C(=O). In further embodiments of the compounds of Formula (I), A, is C(=S). In further embodiments of the compounds of Formula (I), A, is SO_2.

[0159] In further embodiments of the compounds of Formula (I), R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

[0160] In some embodiments of the compounds of Formula (I), R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0161] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 0, n is 0 and A is C(=O), R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

[0162] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 0, n is 0 and A is C(=O), R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0163] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 1, n is 0 and A is C(=O), R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

[0164] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 1, and n is 0, R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0165] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 0, n is 1 and A is C(=O), R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

[0166] In some embodiments of the compounds of Formula (I), where B is L_1, q is 1, m is 0, and n is 1, R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

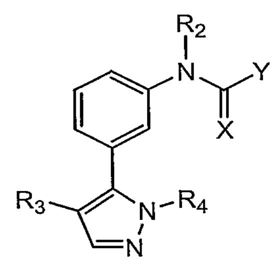
[0167] In some of each of the foregoing embodiments of the compounds of Formula (I), R_2 is H and R_4 is methyl of each of the foregoing embodiments of the compounds of Formula (I), R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2.

[0168] In some embodiments of the compounds of Formula (I), where B is L_1, q is 0, m is 0, and n is 0, A is SO_2. In some of such embodiments, R_2 is H and R4 is methyl. In still further such embodiments, R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0169] In some embodiments of the compounds of Formula (I), B is L_2. In some such embodiments, A is (C=O). In further such embodiments, R_4 is methyl. In still further such embodiments, R_2 is H. In further such embodiments, Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl, butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-

methoxyphenyl, 2-chlorophenyl, -C(CH$_3$)=CH, 1-(N-pyridyl)ethyl, or 9-fluoreneylmethyl. In further such embodiments, R1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH$_3$; and R$_3$ is Cl, Br, I, -COOCH$_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0170] In another aspect of the invention, a series of compounds possessing 5-HT$_{2A}$ receptor activity that are useful as inverse agonists at such receptors is designated by Formula (**A**):



(A)

wherein:

R$_2$ is H or lower alkyl(C$_{1-4}$);

R$_3$ is lower alkyl (C$_{1-6}$), or halogen;

R$_4$ is lower alkyl (C$_{1-6}$);

X is either Oxygen or Sulfur;

Y is NR$_{15}$R$_{16}$, or (CH$_2$)$_m$R$_{17}$, or O(CH$_2$)$_n$R$_{17}$;

m=0-4

n=0-4

R$_{15}$ is H or lower alkyl(C$_{1-4}$);

R$_{16}$ and R$_{17}$ are independently C$_{1-6}$ alkyl, or C$_{2-6}$ alkenyl, or cycloalkyl, or aryl, or CH$_2$ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF$_3$, CCl$_3$, Me, NO$_2$, OH, OMe, OEt, CONR$_{18}$R$_{19}$, NR$_{18}$R$_{19}$, NHCOCH$_3$, OCF$_3$, SMe, COOR$_{20}$, SO$_3$R$_{20}$, SO$_2$NR$_{18}$R$_{19}$, COMe, COEt, CO-lower alkyl, SCF$_3$, CN, C$_{2-6}$ alkenyl, H, halogens, C$_{1-4}$ alkoxy, C$_{3-6}$ cycloalkyl, C$_{1-6}$ alkyl, and aryl;

R$_{18}$ and R$_{19}$ are independently a H or C$_{1-6}$ alkyl, or C$_{2-6}$ alkenyl, or cycloalkyl, or aryl, or CH$_2$ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF$_3$, CCl$_3$, Me, NO$_2$, OH, OMe, OEt, CONR$_{21}$R$_{22}$, NR$_{21}$R$_{22}$, NHCOCH$_3$, OCF$_3$, SMe, COOR$_{23}$, SO$_3$R$_{23}$,

$SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{23}$, $SO_2NR_{21}R_{22}$, SO_3R_{23}, $NHCOCH_3$, COEt, COMe, or halogen;

R_{20} and R_{23} are each independently selected from H or C_{1-6} alkyl;

R_{21} and R_{22} are each independently are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20}, COEt, $NHCOCH_3$, or aryl;

an aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

C_{1-6} alkyl moieties can be straight chain or branched;

optionally substituted C_{1-6} alkyl moieties can be straight chain or branched;

C_{2-6} alkenyl moieties can be straight chain or branched; and

optionally substituted C_{2-6} alkenyl moieties can be straight chain or branched.

[0171] Examples of suitable C_{1-6} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

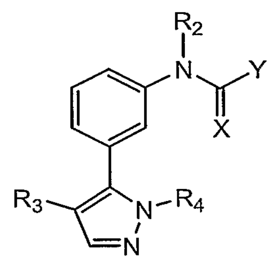
[0172] Halogens are typically F, Cl, Br, and I.

[0173] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalinyl, quinazolinyl and benzothienyl.

[0174] In some embodiments of the foregoing genus (A), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0175] In some embodiments of the foregoing genus (A), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0176] In some preferred embodiments, compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors are designated by the general Formula **A1**:



(A1)

wherein:

R_3 is F, Cl, Br, I, C_{1-6} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-6} alkenyl;

X is O or S;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

m is an integer between 0 and 4, inclusive;

n is an integer between 0 and 4, inclusive;

R_4 is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_2 and R_{15} ais each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_{16} and R_{17} is each independently selected from: C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: H, F, Cl, Br, I, R_{20}, CF_3, CF_2R_7, CF_2CF_2, CCl_3, CCl_2R_7, $CCl_2CCl_2R_7$, $NR_{18}R_{19}$, $NR_{18}COR_{20}$, $NR_{18}SO_2R_{20}$, OR_{20}, OCF_3, OCF_2R_{20}, $OCF_2CF_2R_{20}$, $OCOR_{20}$, OSO_2R_{20}, $OPO(OR_{20})_2$, SR_{20}, SCF_3, SCF_2R_{20}, $SCF_2CF_2R_{20}$, $SCOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, $PO(OR_{20})_3$, $PO(OR_{20})_2R_{20}$, NO_2, CN, $CNR_{20}(NR_{18}R_{19})$, $CNR_{18}(SR_{20})$, $COOR_{20}$, $COSR_{20}$, $CONR_{18}R_{19}$,

with the proviso that when R_{16} or R_{17} contains an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{20} is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, C_{2-8} alkenyl, aryl or alkylaryl;

R_{18} and R_{19} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13}, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that when either or both of R_{18} or R_{19} contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

or

R_{18} or R_{19} may together form part of a 5, 6 or 7 membered cyclic structure, with said structure being saturated or unsaturated, and further with said structure containing up to four heteroatoms selected from O, N or S, and further wherein each moiety within said cyclic structure being optionally substituted by up to four substituents in any position independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that wherein when R_{18} or R_{19} form an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together

be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure.

[0177] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

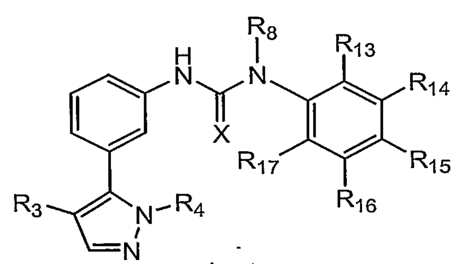
Examples of suitable C_{1-8} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0178] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl, and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalinyl, quinazolinyl, and benzothienyl.

[0179] In some embodiments of the foregoing genus (A), compounds of Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0180] In some embodiments of the foregoing genus (A), compounds of Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0181] Preferred compounds falling within the scope of general Formula (A) as Class (1) compounds where Y = $N_{15}R_{16}$ and has the Formula (**A2**):



(A2)

wherein:

X is O or S;

R_4 is H or CH_3;

R_8 and R_{20} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_{15} is H, F, Cl, Br, I, R_{20}, CF_3, CF_2R_{20}, CF_2CF_2, CCl_3, CCl_2R_{20}, $CCl_2CCl_2R_{20}$, $NR_{18}R_{19}$, $NR_{19}COR_{20}$, $NR_{19}SO_2R_{20}$, OR_{20}, OCF_3, OCF_2R_{20}, $OCF_2CF_2R_{20}$, $OCOR_{20}$, OSO_2R_{20}, $OPO(OR_{20})_2$,

SR_{20}, SCF_3, SCF_2R_{20}, $SCF_2CF_2R_{20}$, $SCOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, $PO(OR_{20})_3$, $PO(OR_{20})_2R_{20}$, NO_2, CN, $CNR_{20}(NR_{18}R_{19})$, $CNR_{19}(SR_{20})$, $COOR_{20}$, $COSR_{20}$, $CONR_{18}R_{19}$,

with the proviso that when a position adjacent to R_{15} is substituted, then R_{15} and said adjacent position can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{18} and R_{19} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that when either or both of R_{18} or R_{19} contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} each independently selected from the following: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

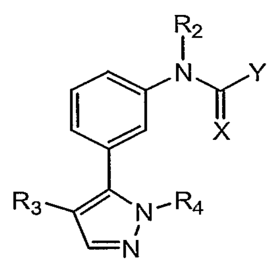
with the proviso that when any two adjacent positions of R_{13}, R_{14}, R_{15}, R_{16} and $R_{17}$are substituted, said two adjacent positions can together be further selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure; and

with the proviso that at least one of R_{13}, R_{14}, R_{15}, R_{16} and R_{17} must be H.

[0182] In some embodiments of the foregoing genus (A), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0183] In some embodiments of the foregoing genus (A), class (1), compounds of Example 13,Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0184] A more preferred series of compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors is designated by the general Formula (**B**):



(B)

wherein:

R_2 is H or lower alkyl (C_{1-4});

R_3 is Me, or Et, or halogen;

X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

R_4 is lower alkyl (C_{1-6});

m=0-4

n=0-4

R_{15} is H or lower alkyl(C_{1-4});

R_{16} and R_{17} are independently C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy

wherein each of the C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl

or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_7$, $SO_2NR_{24}R_{25}$, SO_3R_{26}, $NHCOCH_3$, COEt, COMe, or halogen;

R_{20} and R_{23} are each independently selected from H or C_{1-6} alkyl;

R_{21} and R_{22} are each independently are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20}, COEt, $NHCOCH_3$, or aryl;

C_{1-6} alkyl moieties can be straight chain or branched;

optionally substituted C_{1-6} alkyl moieties can be straight chain or branched:

C_{2-6} alkenyl moieties can be straight chain or branched; and

optionally substituted C_{2-6} alkenyl moieties can be straight chain or branched.

[0185] Examples of suitable C_{1-6} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0186] Halogens are typically F, Cl, Br, and I.

[0187] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl,

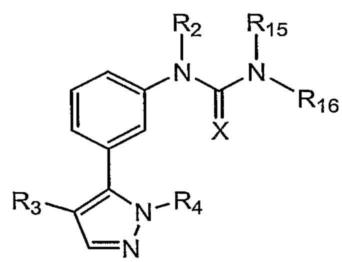
benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalinyl, quinazolinyl and benzothienyl.

[0188] In some embodiments of the foregoing genus (B), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0189] In some embodiments of the foregoing genus (B), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0190] Exemplary compounds of general Formula (A), Class (1) are set forth below. Based upon *in vivo* data developed (as set forth below), Compounds **8** and **9** are particularly preferred.

[0191] A first series of compounds having 5-HT_{2A} receptor activity is represented by a class (I) of compounds of Formula (B) wherein $Y=NR_{15}R_{16}$ and is Formula (**B1**):



(B1)

wherein:

Preferably R_2 and R_{15} are H;

Preferably R_3 is Br;

Preferably X is O;

Preferably R_4 is Me.

In some embodiments of the foregoing genus (B), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

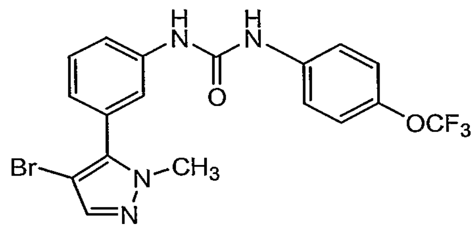
[0192] In some embodiments of the foregoing genus (B), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0193] In reference to Formula (**B1**) R_{16} is preferably 4-trifluoromethoxyphenyl , 4-trifluoromethoxybenzyl, 4-chlorophenyl or 4-fluorophenyl.

[0194] Certain preferred compounds are:

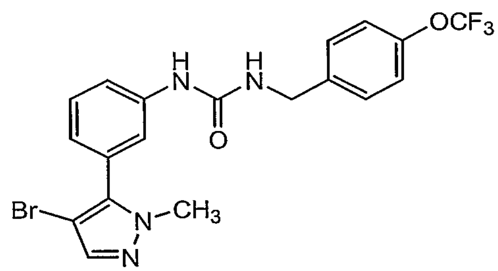
Compound **7**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl)aminocarboxamide



Compound **10**

N-(3-(4-bromo-2-methylpyrazol-3-yl)-phenyl)(((4-trifluoromethoxy)phenylmethyl) Aminocarboxamide



[0195] These two compounds demonstrated the following activities using the assay protocols defined in the Examples above:

TABLE 5

Compound Number	Competitive Binding AP-1 ((^{3}H)mesulergine) IC_{50} Value (μM)	Competitive Binding WT 5-HT_{2A} ((^{3}H)LSD) IC_{50} Value (μM)	Inositol Phosphate Accumulation AP-3 IC_{50} Value (μM)
Compound **7**	2.1	.046	.052
Compound **10**	1.2	.45	.0171

[0196] Additional compounds are set forth below. Inositol phosphate accumulation assays evidence the activity of test compounds. Both single concentration percentages of control values and IC_{50} determinations indicate activity. In the tables below the column legends have the following meanings:

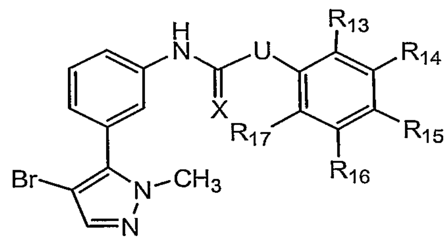
IP_3 % Control: The values in this column reflect an IP Accumulation Assay where the test compounds were evaluated at one concentration of 10 μM. For these assays, the compound was diluted into inositol-free Dulbecco's Eagle Media containing 10 μM pargyline and 10 mM LiCl and tested at a final assay concentration of 10 μM, in triplicate. The percent control value was calculated based on the control in which no test compound was added.

IP_3 AP-3 IC_{50} nM: The values in this column reflect an IP accumulation assay in which the test compound was evaluated at several different concentrations whereby an IC_{50} could be determined. This column corresponds to the column appearing in the tables above which is labeled: Inositol Phosphate Accumulation, AP-3, IC_{50} Value (μM).

WT 5-HT_{2A} LSD IC_{50} nM: The values in this column reflect a competitive binding assay using LSD. This column corresponds to the column appearing in the tables above which is labeled: Competitive Binding, WT 5-HT_{2A}, ((^{3}H)LSD), IC_{50} Value (μM).

[0197] Compounds listed in each of the following tables reference the structures immediately preceding the table. A “dash” in the table indicates that no value was determined.

TABLE 6

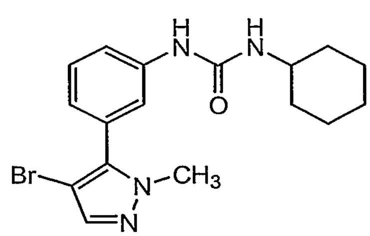


Compound No.	R_{15}	R_{14}	R_{13}	R_{16}	X	U	IP_3 % of Control	IP_3 AP-3 IC_{50} nM	WT 5-HT_{2A} LSD IC_{50} nM
Compound Name									
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino)carboxamide									
Compound **11**	SCH_3	H	H	H	O	NH	16	17	4
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino)carboxamide									
Compound **8**	Cl	H	H	H	O	NH	10	3.2	11
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-fluorophenyl)carboxamide									
Compound **9**	F	H	H	H	O	NH	11	-	7
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide									
Compound **12**	H	H	CF_3O	H	O	NH	11	-	200
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-nitrophenyl)carboxamide									
Compound **13**	H	H	NO_2	H	O	NH	27	-	238
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-methoxyphenyl)carboxamide									
Compound **14**	MeO	H	H	H	O	NH	12	-	19

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl)carboxamide									
Compound **15**	H	H	Me	H	O	NH	32	-	131
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-(trifluoromethyl)phenyl) carboxamide									
Compound **16**	CF_3	H	H	H	O	NH	11	-	65
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-chlorophenyl)carboxamide									
Compound **17**	H	Cl	H	H	O	NH	11	-	39
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-chlorophenyl)carboxamide									
Compound **18**	H	H	Cl	H	O	NH	6	-	249
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)phenyl)carboxamide									
Compound **19**	isopropyl	H	H	H	O	NH	7	-	338
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-methoxyphenyl)carboxamide									
Compound **20**	H	MeO	H	H	O	NH	7	-	106
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-methylphenyl)carboxamide									
Compound **21**	H	Me	H	H	O	NH	14	-	57
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)carboxamide									
Compound **22**	CF_3O	H	H	H	O	NCH_3	-	193	2
N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound **23**	t-butyl	H	H	H	O	NH	17	-	476
N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound **24**	NMe_2	H	H	H	O	NH	9	-	309

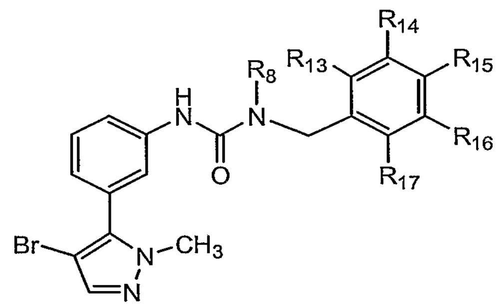
N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound **25**	Me	Cl	H	Cl	O	NH	23	-	122
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-(trifluoromethylthio)phenyl)carboxamide									
Compound **26**	CF_3S	H	H	H	O	NH	12	-	56
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-fluorophenyl)carboxamide									
Compound **27**	H	H	F	H	O	NH	12	-	37
2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino)benzamide									
Compound **27**	H	H	$CONH_2$	H	O	NH	31	-	7473
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-cyanophenyl)carboxamide									
Compound **29**	CN	H	H	H	O	NH	12	-	2
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-cyanophenyl)carboxamide									
Compound **30**	H	H	CN	H	O	NH	30	-	348

TABLE 7



Compound No.		**IP_3 AP-3 IC_{50} nM**	**WT 5-HT_{2A} LSD IC_{50} nM**
Compound **31**	N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(cyclohexylamino)carboxamide	114	81

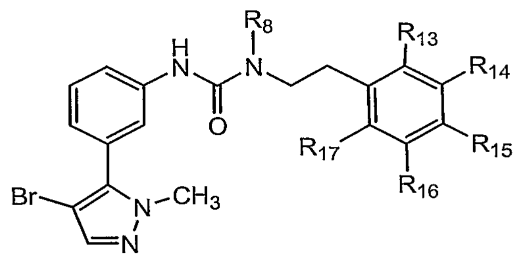
TABLE 8



Compound No.	R_{15}	R_{14}	R_{13}	R_{16}	R_8	IP_3 AP-3 IC$_{50}$ nM	WT 5-HT$_{2A}$ LSD IC$_{50}$ nM
Compound Name							
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(phenylmethylamino)carboxamide							
Compound **32**	H	H	H	H	H	120	47
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((4-fluorophenyl)methyl)amino)carboxamide							
Compound **33**	F	H	H	H	H	89	132
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)- (((3,4-dimethoxyphenyl)methyl)amino)-carboxamide							
Compound **34**	OMe	OMe	H	H	H	-	1010
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((3,4,5-trimethoxyphenyl)methyl)amino)-carboxamide							
Compound **35**	OMe	OMe	H	OMe	H	-	2960

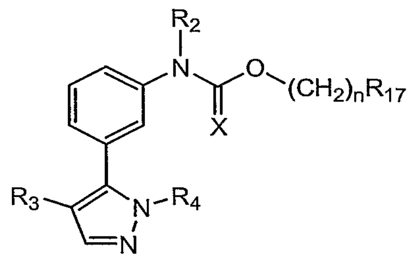
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((2-methylphenyl)methyl)amino)carboxamide							
Compound **36**	H	H	Me	H	H	-	769
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-methoxyphenyl)methyl)amino)carboxamide							
Compound **37**	OMe	H	H	H	H	-	102

TABLE 9



Compound Name							
Compound No.	**R_{15}**	**R_{14}**	**R_{13}**	**R_{16}**	**R_8**	**IP_3 AP-3 IC_{50} nM**	**WT 5-HT_{2A} LSD IC_{50} nM**
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-(4-methoxyphenyl)ethyl)amino)carboxamide							
Compound **38**	OMe	H	H	H	H	32	61

[0198] A second series of compounds having 5-HT_{2A} receptor activity is represented by a class (II) of compounds of formula (B) wherein Y= $O(CH_2)_nR_{17}$.



(B2)

wherein:

Preferably R_2 is H.

Preferably R_3 is Br.

Preferably X is O.

Preferably R_4 is Me.

Preferably when n = 0, R_{17} is 4-methoxyphenyl or tertiary butyl.

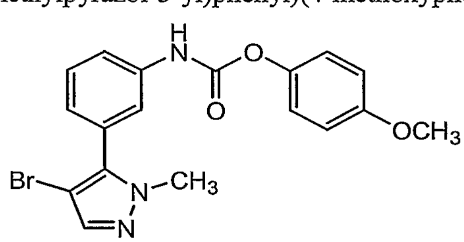
In some embodiments of the foregoing genus (B), class (II), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0199] In some embodiments of the foregoing genus (B), class (II) compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0200] Certain preferred compounds are: .

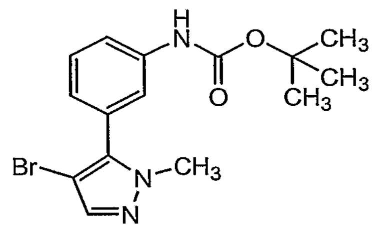
Compound **1**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide



Compound **39**

(tert-butoxy)-N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)carboxamide



[0201] Compounds **1** and **39** demonstrated the following activity as illustrated in TABLE 10:

TABLE 10

Compound Number	Competitive Binding AP-1 ((^{3}H)mesulergine) IC_{50} Value (μM)	Competitive Binding WT 5-HT_{2A} ((^{3}H)LSD) IC_{50} Value (μM)	Inositol Phosphate Accumulation AP-3 IC_{50} Value (μM)
Compound **1**	1.8	<0.001	0.0003
Compound **39**	-	0.014	0.057

[0202] In addition to the assays discussed above, the specific activity of Compound **1** at the 5-HT_{2A} receptor was further confirmed by the following:

<u>In Vitro Binding of 5-HT_{2A} Receptor</u>

<u>Animals:</u>

[0203] Animals (Sprague-Dawley rats) were sacrificed and brains were rapidly dissected and frozen in isopentane maintained at –42° C. Horizontal sections were prepared on a cryostat and maintained at -20 ° C.

<u>LSD Displacement Protocol:</u>

[0204] Lysergic acid diethylamide (LSD) is a potent 5-HT_{2A} receptor and dopamine D2 receptor ligand. An indication of the selectivity of compounds for either or both of these receptors involves displacement of radiolabeled-bound LSD from pre-treated brain sections. For these studies, radiolabeled I^{125}-LSD (NEN Life Sciences, Boston, Mass., Catalogue number NEX-199) was utilized; spiperone (RBI, Natick, Mass. Catalogue number s-128) a 5-HT_{2A} receptor and dopamine D2 receptor antagonist, was also utilized. Buffer consisted of 50 nanomolar TRIS-HCl, pH 7.4.

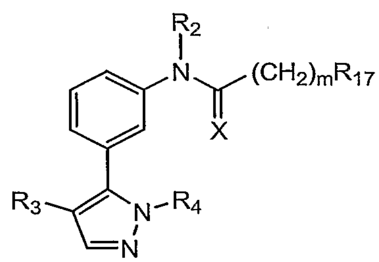
[0205] Brain sections were incubated in (a) Buffer plus 1 nanomolar I^{125}-LSD; (b) Buffer plus 1 nanomolar I^{125}-LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar I^{125}-LSD and 1 micromolar Compound **1** for 30 minutes at room temperature. Sections were then washed 2x 10 minutes at 4 ° C. in Buffer, followed by 20 seconds in distilled H_2O. Slides were then air-dried.

[0206] After drying, sections were apposed to x-ray film (Kodak Hyperfilm) and exposed for 4 days.

Analysis:

[0207] Figures 16A-C provide representative autoradiographic sections from this study. Figure 16A evidences darker bands (derived from I^{125} -LSD binding) primarily in both the fourth layer of the cerebral cortex (primarily 5-HT_{2A} receptors), and the caudate nucleus (primarily dopamine D2 receptors and some 5-HT_{2A} receptors). As can be seen from Figure 16B, spiperone, which is a 5-HT_{2A} and dopamine D2 antagonist, displaces the I^{125}-LSD from these receptors on both the cortex and the caudate. As can be further seen from Figure 16C, Compound **1** appears to selectively displace the I^{125}-LSD from the cortex (5-HT_{2A}) and not the caudate (dopamine D2).

[0208] A third series of compounds having 5-HT_{2A} receptor activity is represented by a class (III) of compounds of Formula (**B3**) wherein Y=$(CH_2)_mR_{17}$:



(B3)

wherein

Preferably R_2 is H.

Preferably R_3 is Br.

Preferably X is O.

Preferably R_4 is Me.

[0209] Preferably when m= 0, R_{17} is preferably 4-trifluoromethoxyphenyl, or thiophene, or 4-chlorophenyl.

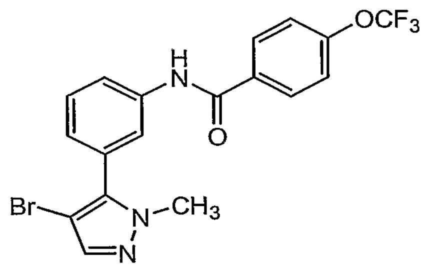
[0210] In some embodiments of the foregoing genus (B), class (III), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0211] In some embodiments of the foregoing genus (B), class (III) compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0212] Certain preferred compounds are:

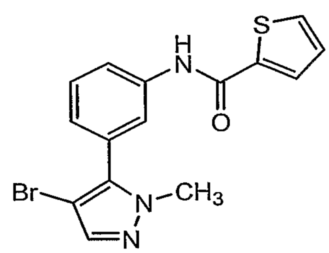
Compound **40** (m = 0, R_2 = H, R_{17} = 4-trifluoromethoxyphenyl)

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethoxy-benzamide



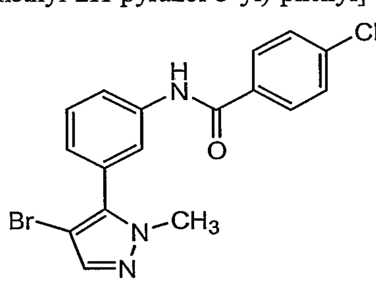
Compound **2** (m=0, R_2= H, R_{17} = thiophene)

Thiophene-2-carboxylic acid [3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]amide



Compound **41** (m=0, R_2= H, R_{17} = chlorophenyl)

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-4-chloro-benzamide



[0213] These three compounds demonstrated the following activities:

TABLE 11

Compound Number	Competitive Binding AP-1 ((^{3}H)mesulergine) IC_{50} Value (μM)	Competitive Binding WT 5-HT_{2A} ((^{3}H)LSD) IC_{50} Value (μM)	Inositol Phosphate Accumulation AP-3 IC_{50} Value (μM)
Compound **40**	6.1	.46	0.0213
Compound **2**	2.8	.17	0.080
Compound **41**	1.2	.21	0.0315

In Vivo Analysis of Compound 2

[0214] In addition to the in vitro assays shown in the above table, the in vivo response of animals to Compound 2 is demonstrated by the following.

[0215] A 5-HT_{2A} receptor antagonist or inverse agonist is expected to decrease amphetamine-stimulated locomotion without affecting baseline locomotion. See, for example, Soresnon, et al, 266(2) J. Pharmacol. Exp. Ther. 684 (1993). Based upon the foregoing information, Compound 2 is a potent inverse agonist at the human 5-HT_{2A} receptor. For the following study, the following parameters and protocol were utilized:

Animals, Vehicle

[0216] Adult male Sprague-Dawley rats were utilized for these studies. Animals were housed in groups of 2-3 in hanging plastic cages with food and water available at all times. Animals were weighed and handled for at least one day prior to surgery and throughout the studies. For these studies, Vehicle consisted of 90% ethanol (100%) and 10% water.

Amphetamine-Stimulated Locomotor Activity: Assessment and Apparatus

[0217] A San Diego Instruments Flex Field apparatus was used to quantify baseline and amphetamine-stimulated locomotor activity. This apparatus consists of four 16" x 16" clear plastic open fields. Photocell arrays (16 in each dimension) interfaced with a personal computer to automatically quantify activity. Several measures of activity can be assessed with the apparatus, including total photocell beam breaks. Animals (vehicle control and Compound treated) were injected

s.c. 30 minutes prior to initiation of analysis. Following this 30 minute period, animals were placed individually into an open field and baseline activity was assessed for 30 minutes (habituation phase). Following baseline, animals were removed, injected with d-amphetamine sulfate (1.0 mg/kg) and immediately returned to the open field for 150 minutes, in order to follow the time course (10 minute intervals) of amphetamine-stimulated locomotor activity.

Dosing

TABLE 12

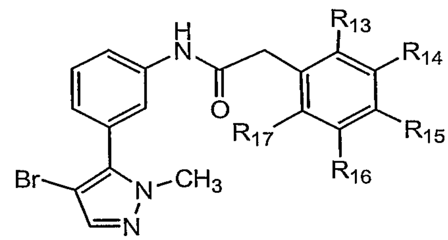
Vehicle Control	Compound 2	Dose (mg/kg)
6 animals	6 animals	0.1
	6 animals	1.0
	6 animals	5.0
	6 animals	10.0

Analysis

[0218] Results, based upon the number of recorded photobeam breaks (mean.+/-sem), are presented in Figures 17A-C. As supported by Figures 17A, B and C, a general "inverted U" shaped pattern was observed (see, generally, Sahgal, A. "Practical behavioural neuroscience: problems, pitfalls and suggestions" pp 1-8, 5 in Behavioral Neuroscience: A Practical Approach, Volume 1 A. Sahgal (Ed.) 1993, IRL Press, New York). As Figure 17 also indicates, with exception of the highest dose (10 mg/kg), in vivo, the tested doses of Compound 2 evidenced a decrease in the amphetamine-stimulated locomotion, consistent with a 5-HT_{2A} receptor antagonist or inverse agonist.

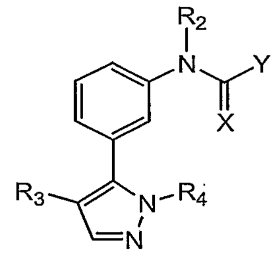
[0219] Additional series of compounds of Formula (B) wherein $Y=(CH_2)_mR_{17}$ are set forth below in TABLE 13.

TABLE 13



Name	Compound No.	R_{15}	R_{14}	R_{13}	R_{16}	IP_3 AP-3 IC_{50} nM	WT 5-HT_{2A} LSD IC_{50} nM
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy)-phenyl)acetamide	Compound **42**	OCF_3	H	H	H	-	106
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(3-Fluorophenyl)acetamide	Compound **43**	H	F	H	H	153	318
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(3-Methoxyphenyl)acetamide	Compound **44**	H	OMe	H	H	108	625
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(2-Fluorophenyl)acetamide	Compound **45**	H	H	F	H	129	662
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(4-Nitrophenyl)acetamide	Compound **46**	NO_2	H	H	H	61	108
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(2-Methoxyphenyl)acetamide	Compound **47**	H	H	OMe	H	165	2300

[0220] Based upon the discovery of the specific inverse agonist activity of the above identified compounds at the 5-HT_{2A} receptor, a novel class of compounds has been identified which exhibits said activity. Accordingly, in the second aspect of the invention, there is provided a novel compound of formula **(C)**:



(C)

wherein:

R^2 is H or lower alkyl(C_{1-4});

R_3 is Me, or Et, or halogen;

X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH2)_m$ R_{17}, or $O(CH_2)_n$ R_{17};

R_4 is lower alkyl (C_{1-6});

m=0-4;

n=0-4;

R_{15} is H or lower alkyl(C_{1-4});

R_{16} is a C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or $(CH_2)_k$ aryl group (k=1-4), preferably k=1, and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy may be further substituted by up to four substitutents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$,

COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_7$, $SO_2NR_{21}R_{22}$, SO_3R_{23}, $NHCOCH_3$, COEt, COMe, or halogen;

R_{17} is C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

R_{20} and R_{23} may be independently selected from H or C_{1-6} alkyl;

R^{21} and R^{22} are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20}, COEt, $NHCOCH_3$, or aryl. An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

C_{1-6} alkyl moieties can be straight chain or branched;

optionally substituted C_{1-6} alkyl moieties can be straight chain or branched;

C_{2-6} alkenyl moieties can be straight chain or branched; and

optionally substituted C_{2-6} alkenyl moieties can be straight chain or branched;

Examples of suitable C_{1-6} alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0221] Halogens are typically F, Cl, Br, and I.

[0222] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl,

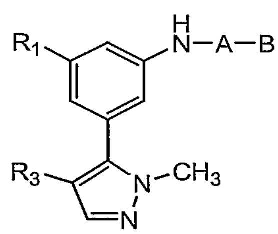
thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalinyl, quinazolinyl and benzothienyl.

[0223] In some embodiments of the foregoing genus (C), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0224] In some embodiments of the foregoing genus (C), compounds of Example, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0225] Some embodiments of the invention are compounds of Formula (V) and have one of the structures below.

TABLE 14



(V)

Cmpd	R_1	R_3	A	B
Compound Name				
48	H	Cl	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
49	Cl	Cl	C(=O)	-NH-(4-chlorophenyl)
1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
50	H	Cl	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea				
51	H	Cl	C(=O)	-NH-CH(CH_3)-phenyl
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea				
52	H	Cl	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea				

53	H	Cl	C(=O)	-NH-(4-dimethylaminophenyl
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea				
54	H	Cl	C(=O)	-NH-(4-ethoxycarbonyl)phenyl
4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester				
55	H	Cl	C(=O)	-NH-(4-methylthio)phenyl
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea				
56	H	Cl	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
57	H	I	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
58	H	Br	C(=O)	-O-ethyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester				
59	H	Br	C(=O)	-O-(4-nitro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester				
60	H	Br	C(=O)	-O-CH_2-fluorene-9-yl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester				
61	H	Br	C(=O)	-O-$CH_2CH=CH_2$
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester				
62	H	Br	C(=O)	-O-(4-methyl)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester				
63	H	Br	C(=O)	-O-n-butyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester				
64	H	Br	C(=O)	-O-(2-isopropyl-5-methyl)cyclohex-1-yl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester				
65	H	Br	C(=O)	-O-benzyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester				
66	H	Br	C(=O)	-O-(3-trifluoromethyl)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester				

67	H	Br	C(=O)	-O-(4-bromo)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester				
68	H	Br	C(=O)	-O-(4-fluoro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester				
69	H	Br	C(=O)	-O-(2-methoxy)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester				
70	H	Br	C(=O)	-O-(2-chloro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester				
71	H	Br	C(=O)	-O-C(CH_3)=CH_2
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester				
72	H	Br	C(=O)	-O-1-(N-pyridinyl)ethyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl ester				
73	H	Br	C(=O)	-O-isopropyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester				
74	H	-C(=O)OCH_3	C(=O)	-NH-(4-chlorophenyl)
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid methyl ester				
75	H	-CH_2CH_2OH	C(=O)	-NH-(4-fluorophenyl)
1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
76	H	-$CH_2CH_2N(Me)_2$	C(=O)	-NH-(4-fluorophenyl)
1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-phenyl)-urea				
77	H	-CH=CH_2	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea				
78	H	CH_2CH_3	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
79	H	-CH=CH_2	C(=O)	-NH-(4-fluorophenyl)
1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea				
80	H	Phenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea				
81	H	4-methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
82	H	3-methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				

83	H	4-fluorophenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
84	H	4-trifluoro methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-phenyl}-urea				
85	H	Thiophen-2-yl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea				
86	H	-C(=O)-OH	C(=O)	-NH-(4-chlorophenyl)
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid				
87	H	Cyclopropyl	C(=O)	-NH-(3-trifluoromethylphenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea				
88	H	Cyclopropyl	C(=O)	-NH-(3-chlorophenyl)
1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
89	H	Cyclopropyl	C(=O)	-NH-(2-methoxyphenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea				
90	H	-CCH	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
91	H	-CH=CH-CCH	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
92	H	-CH=CH-CCH	C(=O)	-NH-(4-methylphenyl)
1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea				
93	H	CN	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
94	H	CN	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
95	H	Cyclopropyl	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea				
96	F	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea				
97	F	Br	SO_2	4-fluorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-benzenesulfonamide				

98	F	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea				
99	F	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea				
100	F	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea				
101	F	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea				
102	F	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea				
103	F	Br	SO_2	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-benzenesulfonamide				
104	F	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-urea				
105	$-N(Me)_2$	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-phenyl)-urea				
106	Pyrrolidin-1-yl	Br	C(=O)	$-NH-CH(CH_3)$–phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea				
107	Morpholin-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea				
108	Pyrrolidin-1-yl	Br	C(=O)	Phenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide				
109	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-phenyl)-urea				
110	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-dimethylamino-phenyl)-urea				
111	Morpholin-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-phenyl)-urea				

112	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-bromo-phenyl)-urea				
113	-N(Me)$_2$	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-phenyl)-urea				
114	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2-trifluoromethoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-trifluoromethoxy-phenyl)-urea				
115	Pyrrolidin-1-yl	Br	C(=S)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-thiourea				
116	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
117	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
118	Pyrrolidin-1-yl	Br	SO$_2$	4-fluorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluoro-benzenesulfonamide				
119	-N(Me)$_2$	Br	SO$_2$	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chloro-benzenesulfonamide				
120	Morpholin-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluoro-phenyl)-urea				
121	Morpholin-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chloro-phenyl)-urea				
122	Pyrrolidin-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea				

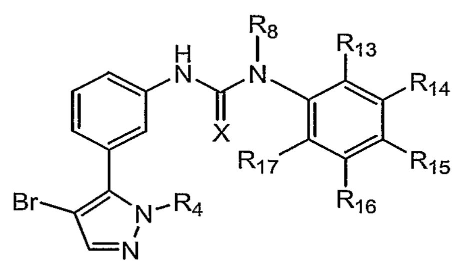
123	-N(Me)$_2$	Br	C(=O)	-NH-(4-dimethylamnophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea				
124	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea				
125	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea				
126	Morpholin-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
127	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea				
128	Morpholin-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-urea				
129	-N(Me)$_2$	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-urea				
130	-N(Me)$_2$	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-phenyl)-urea				
131	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-urea				
132	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
133	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea				

134	Morpholin-1-yl	Br	C(=O)	-NH-(4-trifluoromethylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea				
135	Pyrrolidin-1-yl	Br	C(=O)	-NH-(3-amino-4-fluorophenyl)
1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-urea				
136	-N(Me)$_2$	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-phenyl)-urea				
137	Pyrrolidin-1-yl	Br	C(=O)	-NH-(3-nitro-4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-phenyl)-urea				
138	-N(Me)$_2$	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-urea				
139	Pyrrolidin-1-yl	Br	C(=O)	-NH-CH(CH$_3$) –phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea				
140	Pyrrolidin-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
141	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-urea				
142	Morpholin-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-phenyl)-urea				
143	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-urea				
144	-N(Me)$_2$	Br	SO$_2$	4-fluorophenyl)
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-benzenesulfonamide				
145	Pyrrolidin-1-yl	Br	SO$_2$	Phenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzenesulfonamide				
146	Morpholin-1-yl	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-phenyl)-urea				

147	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea				
148	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-phenyl)-urea				
149	-OMe	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea				
150	-OH	Br	C(=O)	-NH-(3,5-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-urea				
151	-OH	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea				
152	-OMe	Br	SO_2	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-benzenesulfonamide				
153	-OMe	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-phenyl)-urea				
154	-OMe	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea				
155	-OH	Br	SO_2	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-benzenesulfonamide				
156	-OMe	Br	C(=O)	-NH-(3,5-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-urea				
157	-OH	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea				
158	-OMe	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea				
159	-OMe	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-urea				
160	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-trifluoromethyl)phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea				

161	-OH	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-urea				
162	-OMe	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-urea				
163	-OH	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea				
164	H	Br	C(=S)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea				

[0226] Also provided in accordance with the present invention are compounds useful as inverse agonists for 5-HT_{2A} receptors having the structure:



wherein:

X is O or S;

R_4 is H or CH_3;

$\mathbf{R_8}$ and $\mathbf{R_{30}}$ are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

$\mathbf{R_{15}}$ is H, F, Cl, Br, I, R_{20}, CF_3, CCl_3, $NR_{18}R_{19}$, $NR_{30}COR_{20}$, $NR_{30}SO_2R_{20}$, OR_{20}, OCF_3, $OCOR_{20}$, OSO_2R_{20}, SR_{20}, SCF_3, $SCOR_{20}$, SO_3R_{20}, $SO_2NR^8R^9$, NO_2, CN, $COOR_{20}$, $COSR_{20}$, or $CONR_{18}R_{19}$,

with the proviso that when a position adjacent to $\mathbf{R_{15}}$ is substituted, then $\mathbf{R_{15}}$ and said adjacent position can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

$\mathbf{R_{20}}$ is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, C_{2-8} alkenyl, aryl or alkylaryl;

$\mathbf{R_{18}}$ and $\mathbf{R_{19}}$ are each independently selected from: H, C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$,

NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13}, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$,

with the proviso that when either of $\mathbf{R_{18}}$ or $\mathbf{R_{19}}$ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently selected from the following: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13}, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

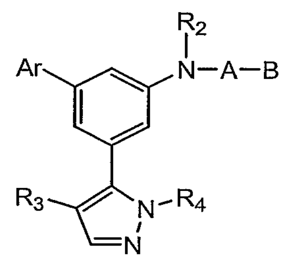
with the proviso that when any two adjacent positions of R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are substituted, said two adjacent positions can together be further selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

with the proviso that at least two of R_{13}, R_{14}, R_{15}, R_{16} and R_{17} must be H.

[0227] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0228] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0229] In some embodiments, compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors are designated by the general Formula **(XV)**:



(XV)

wherein:

i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR_7, OH, NR_8R_9, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl -$C(p)_3$, or -O-$C(p)_3$ where p is halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl; or

R_8 and R_9 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_7 is H or C_{1-6} alkyl;

R_{10} is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, -$C(p)_3$, or -O-$C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can

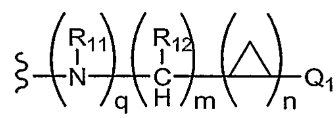
alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



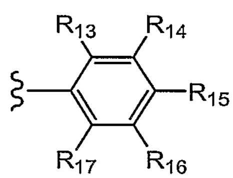
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

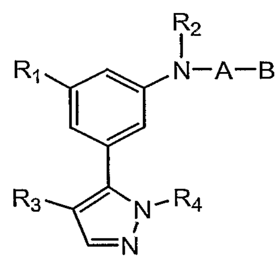
L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl,

alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt.

Methods

[0230] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(I)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen,

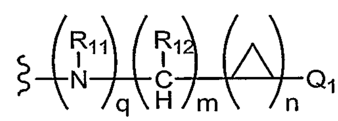
$-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



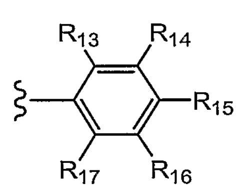
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, -C(p)$_3$, or -O-C(p)$_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

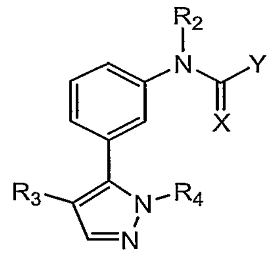
L_2 is –O-Q_2 wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, -C(p)$_3$, or -O-C(p)$_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or
a pharmaceutically acceptable salt.

[0231] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0232] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0233] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0234] Also provided by the present invention are methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(A)

wherein:

R_2 is H or lower alkyl(C_{1-4});

R_3 is lower alkyl (C_{1-6}), or halogen;

R_4 is lower alkyl (C_{1-6});

X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

m=0-4

n=0-4

R_{15} is H or lower alkyl(C_{1-4});

R_{16} and R_{17} are independently C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{23}$, $SO_2NR_{21}R_{22}$, SO_3R_{23}, $NHCOCH_3$, COEt, COMe, or halogen;

R_{20} and R_{23} are each independently selected from H or C_{1-6} alkyl;

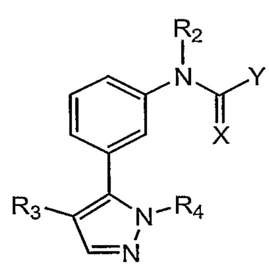
R_{21} and R_{22} are each independently are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20}, COEt, $NHCOCH_3$, or aryl;

an aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0235] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0236] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0237] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(A1)

wherein:

R_3 is F, Cl, Br, I, C_{1-6} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-6} alkenyl;

X is O or S;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

m is an integer between 0 and 4, inclusive;

n is an integer between 0 and 4, inclusive;

R_4 is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_2 and R_{15} ais each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_{16} and R_{17} is each independently selected from: C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: H, F, Cl, Br, I, R_{20}, CF_3, CF_2R_7, CF_2CF_2, CCl_3, CCl_2R_7, $CCl_2CCl_2R_7$, $NR_{18}R_{19}$, $NR_{18}COR_{20}$, $NR_{18}SO_2R_{20}$, OR_{20}, OCF_3, OCF_2R_{20}, $OCF_2CF_2R_{20}$, $OCOR_{20}$, OSO_2R_{20}, $OPO(OR_{20})_2$, SR_{20}, SCF_3, SCF_2R_{20}, $SCF_2CF_2R_{20}$, $SCOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, $PO(OR_{20})_3$, $PO(OR_{20})_2R_{20}$, NO_2, CN, $CNR_{20}(NR_{18}R_{19})$, $CNR_{18}(SR_{20})$, $COOR_{20}$, $COSR_{20}$, $CONR_{18}R_{19}$,

with the proviso that when R_{16} or R_{17} contains an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{20} is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, C_{2-8} alkenyl, aryl or alkylaryl;

R_{18} and R_{19} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that when either or both of R_{18} or R_{19} contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

or

R_{18} or R_{19} may together form part of a 5, 6 or 7 membered cyclic structure, with said structure being saturated or unsaturated, and further with said structure containing up to four heteroatoms

selected from O, N or S, and further wherein each moiety within said cyclic structure being optionally substituted by up to four substituents in any position independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

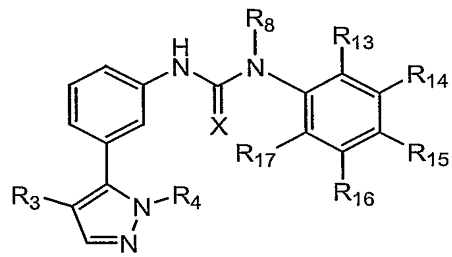
with the proviso that wherein when R_{18} or R_{19} form an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure.

[0238] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0239] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0240] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0241] Also provided by the present invention are methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(A2)

wherein:

X is O or S;

R_4 is H or CH_3;

R_8 and R_{20} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_{15} is H, F, Cl, Br, I, R_{20}, CF_3, CF_2R_{20}, CF_2CF_2, CCl_3, CCl_2R_{20}, $CCl_2CCl_2R_{20}$, $NR_{18}R_{19}$, $NR_{19}COR_{20}$, $NR_{19}SO_2R_{20}$, OR_{20}, OCF_3, OCF_2R_{20}, $OCF_2CF_2R_{20}$, $OCOR_{20}$, OSO_2R_{20}, $OPO(OR_{20})_2$, SR_{20}, SCF_3, SCF_2R_{20}, $SCF_2CF_2R_{20}$, $SCOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, $PO(OR_{20})_3$, $PO(OR_{20})_2R_{20}$, NO_2, CN, $CNR_{20}(NR_{18}R_{19})$, $CNR_{19}(SR_{20})$, $COOR_{20}$, $COSR_{20}$, $CONR_{18}R_{19}$,

with the proviso that when a position adjacent to R_{15} is substituted, then R_{15} and said adjacent position can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{18} and R_{19} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH_2aryl, wherein each moiety within said C_{1-8} straight chain or branched alkyl, C_{2-8} alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH_2aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that when either or both of R_{18} or R_{19} contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure;

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} each independently selected from the following: F, Cl, Br, I, CF_3, CCl_3, CH_3, C_2H_5, C_3H_7, C_4H_9, NH_2, $NHCH_3$, $N(CH_3)_2$, NHC_2H_5, $N(C_2H_5)_2$, NHC_3H_7, $N(C_3H_7)_2$, NHC_4H_9, $N(C_4H_9)_2$, NHCOH, $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_4H_9$, $NHSO_2CH_3$, $NHSO_2C_2H_5$, $NHSO_2C_3H_7$, $NHSO_2C_4H_9$, OH, OCH_3, OC_2H_5, OC_3H_7, OC_4H_7, OC_4H_9, OC_5H_9, OC_5H_{11}, OC_6H_{11}, OC_6H_{13}, OCF_3, $OCOCH_3$, $OCOC_2H_5$, $OCOC_3H_7$, $OCOC_4H_9$, OSO_2CH_3, $OSO_2C_2H_5$, $OSO_2C_3H_7$, $OSO_2C_4H_9$, SH, SCH_3, SC_2H_5, SC_3H_7, SC_4H_7, SC_4H_9, SC_5H_9, SC_5H_{11}, SC_6H_{11}, SC_6H_{13},, SCF_3, $SCOCH_3$, $SCOC_2H_5$, $SCOC_3H_7$, $SCOC_4H_9$, SO_3CH_3, $SO_3C_2H_5$, $SO_3C_3H_7$, $SO_3C_4H_9$, SO_2NH, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, $SO_2NHC_2H_5$, $SO_2N(C_2H_5)_2$, $SO_2NHC_3H_7$, $SO_2N(C_3H_7)_2$, $SO_2NHC_4H_9$, $SO_2N(C_4H_9)_2$, NO_2, CN, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, $COOC_4H_9$, $COSCH_3$, $COSC_2H_5$, $COSC_3H_7$, $COSC_4H_9$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, $CONHC_2H_5$, $CON(C_2H_5)_2$, $CONHC_3H_7$, $CON(C_3H_7)_2$, $CONHC_4H_9$, $CON(C_4H_9)_2$, and

with the proviso that when any two adjacent positions of R_{13}, R_{14}, R_{15}, R_{16} and $R_{17}$are substituted, said two adjacent positions can together be further selected from SCH_2S, SCH_2CH_2S, OCH_2O, or OCH_2CH_2O to form a bi-cyclic structure; and

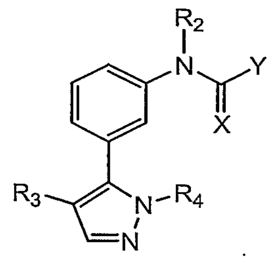
with the proviso that at least one of R_{13}, R_{14}, R_{15}, R_{16} and R_{17} must be H.

[0242] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0243] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0244] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0245] The present invention further provides methods for modulating the activity of a human $5\text{-}HT_{2A}$ serotonin receptor by contacting the receptor with a compound of formula:



(B)

wherein:

R_2 is H or lower alkyl (C_{1-4});

R_3 is Me, or Et, or halogen;

X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

R_4 is lower alkyl (C_{1-6});

m=0-4

n=0-4

R_{15} is H or lower alkyl(C_{1-4});

R_{16} and R_{17} are independently C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{20}$, SO_3R_{20}, $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy wherein each of the C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3, SMe, $COOR_{23}$, SO_3R_{23}, $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl

or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up

to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_7$, $SO_2NR_{24}R_{25}$, SO_3R_{26}, $NHCOCH_3$, COEt, COMe, or halogen;

R_{20} and R_{23} are each independently selected from H or C_{1-6} alkyl;

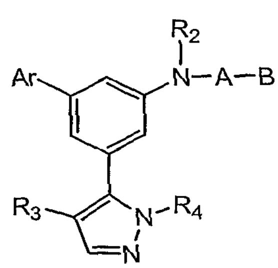
R_{21} and R_{22} are each independently are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20}, COEt, $NHCOCH_3$, or aryl.

[0246] An aryl moiety can be a 5 or 6 membered aromatic hetero-cyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0247] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0248] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0249] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(XV)

wherein:

ii) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR_7, OH, NR_8R_9, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl $-C(p)_3$, or $-O-C(p)_3$ where p is halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3,

OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl; or

R_8 and R_9 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_7 is H or C_{1-6} alkyl;

R_{10} is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

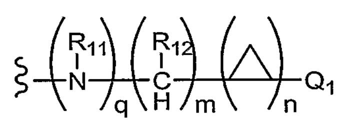
iv) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



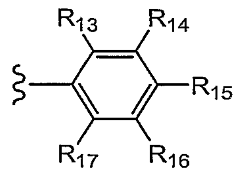
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:

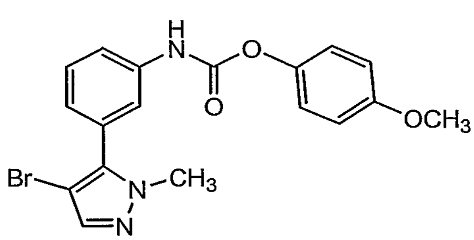


wherein:

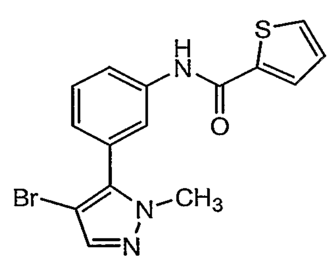
R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, -C(p)$_3$, or -O-C(p)$_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is –O-Q_2 wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, -C(p)$_3$, or -O-C(p)$_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

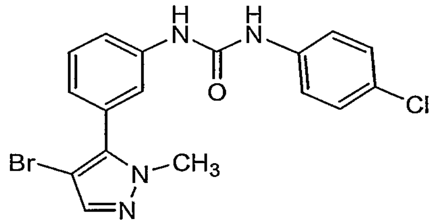
[0250] In some embodiments of the foregoing methods, the compounds are selected from compounds and combinations and subcombinations of compounds selected from the group consisting of:



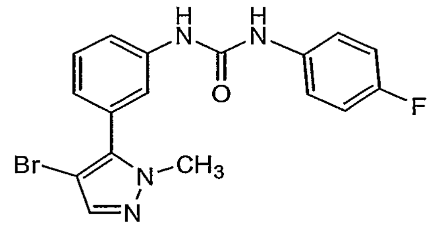
Compound **1**



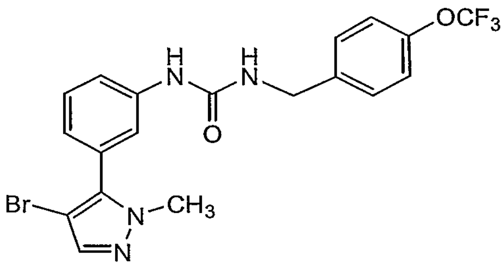
Compound **2**



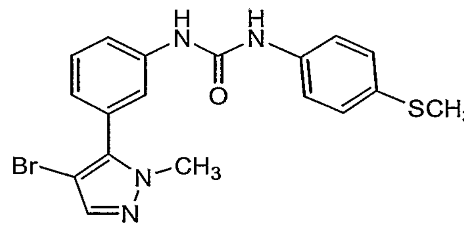
Compound **8**



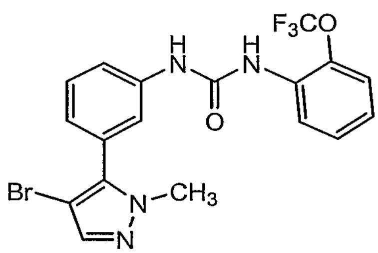
Compound **9**



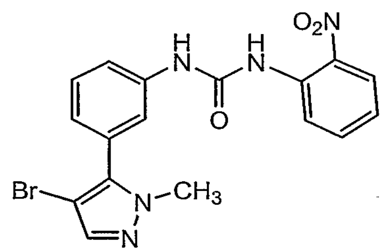
Compound **10**



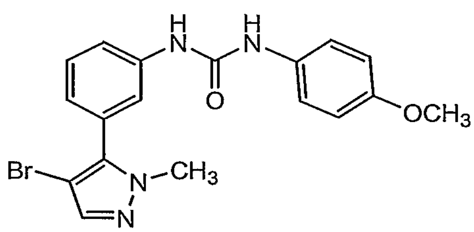
Compound **11**



Compound **12**



Compound **13**



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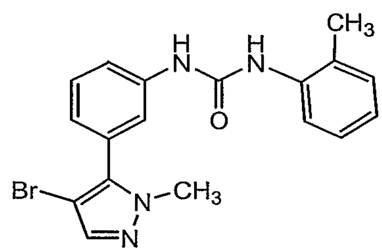
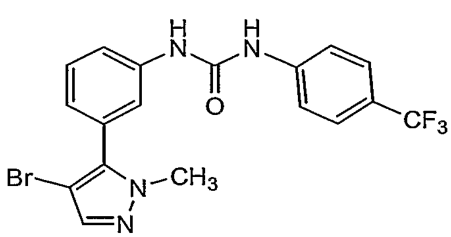
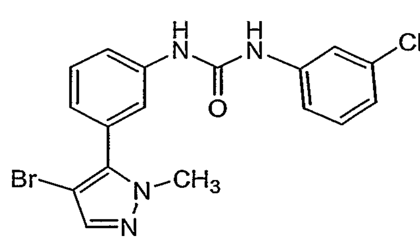


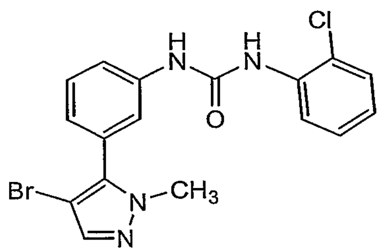
Compound **15**



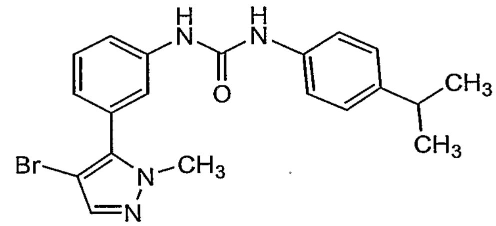
Compound **16**



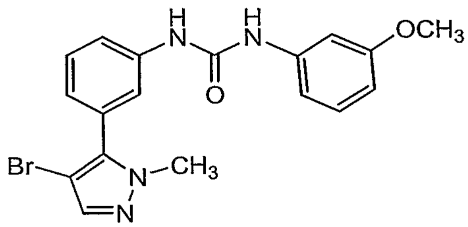
Compound **17**



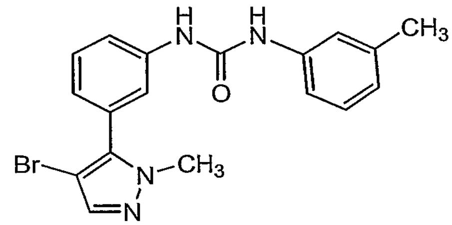
Compound **18**



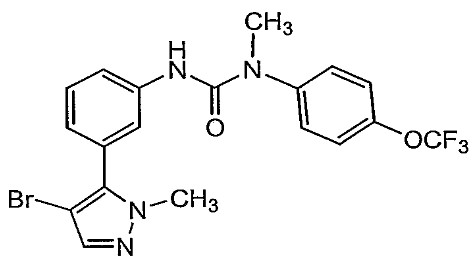
Compound **19**



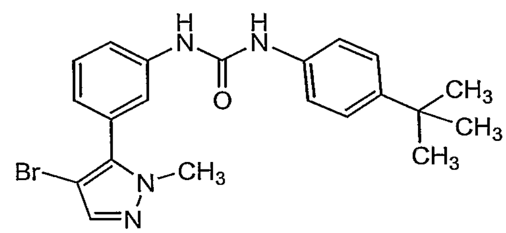
Compound **20**



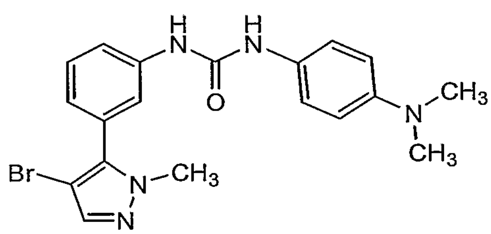
Compound **21**



Compound **22**



Compound **23**



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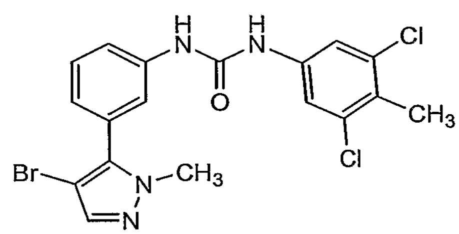
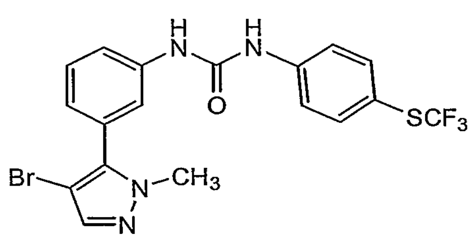
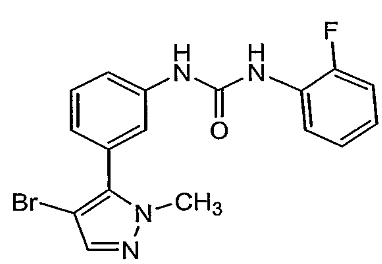


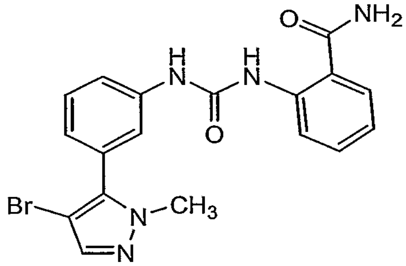
Compound **25**



Compound **26**



Compound **27**



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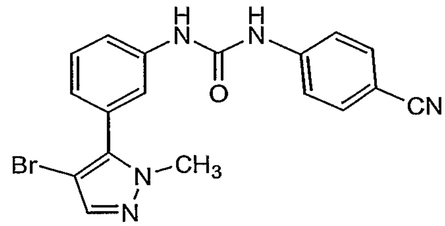
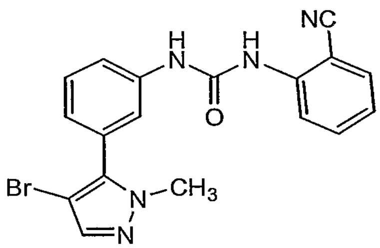
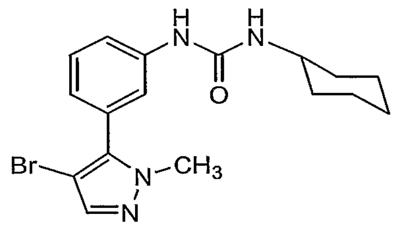


Compound **29**



Compound **30**



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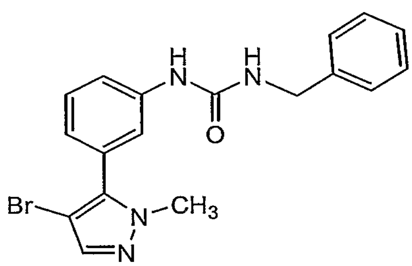

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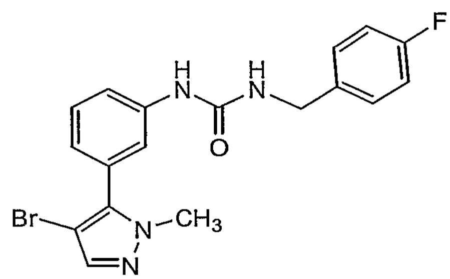
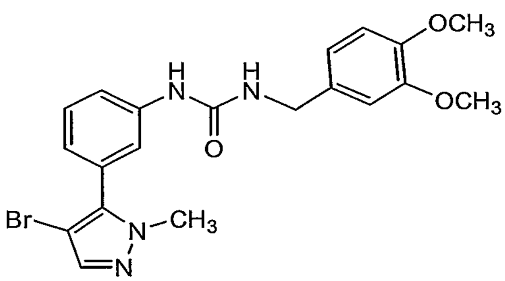
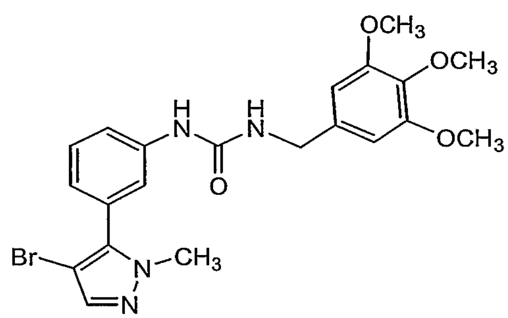


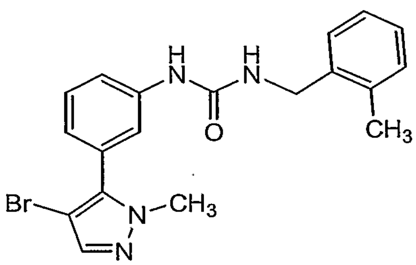
Compound **33**



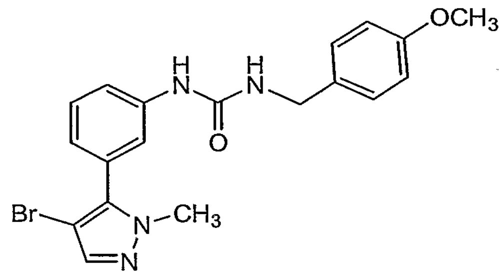
Compound **34**



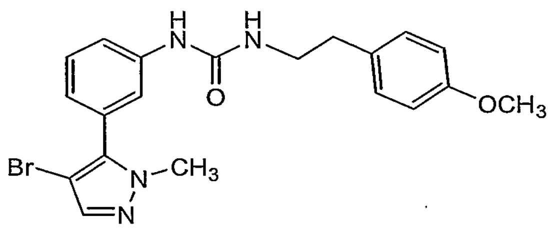
Compound **35**



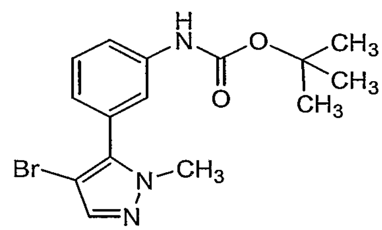
Compound **36**



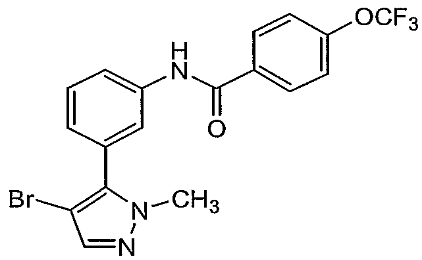
Compound **37**



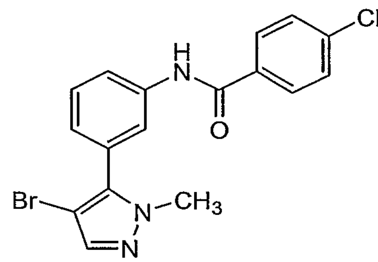
Compound **38**



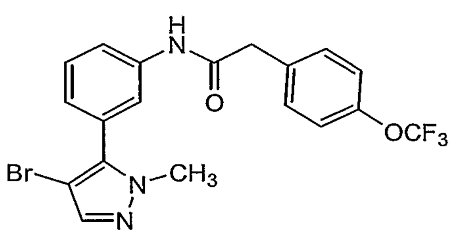
Compound **39**



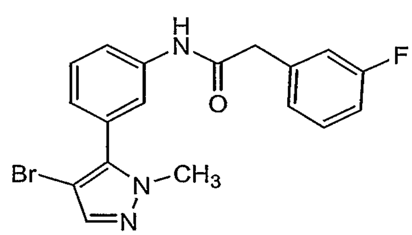
Compound **40**



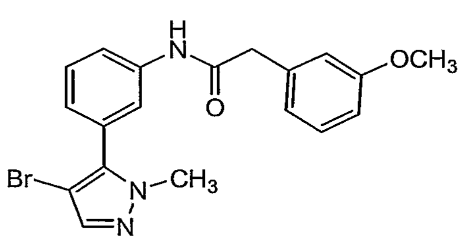
Compound **41**



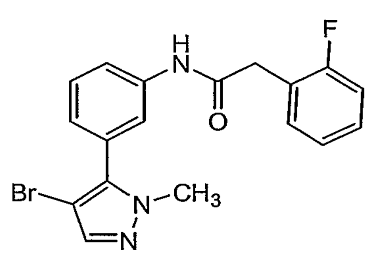
Compound **42**



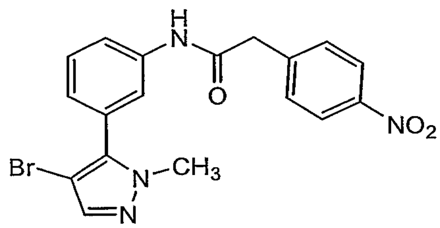
Compound **43**



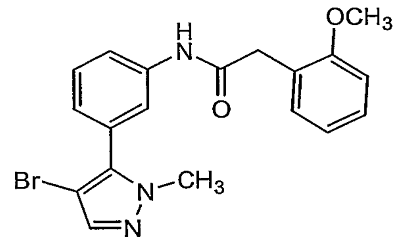
Compound **44**



Compound **45**



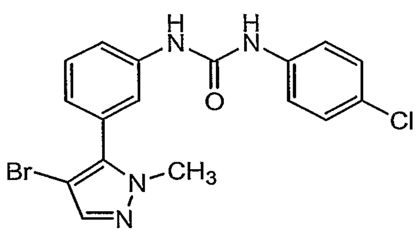
Compound **46**



Compound **47**

[0251] In some embodiments, the present invention provides the foregoing compounds, and combinations and subcombinations thereof.

[0252] In some preferred embodiments, the present invention provides compounds useful as inverse agonists for 5-HT_{2A} receptors structurally represented as follows:



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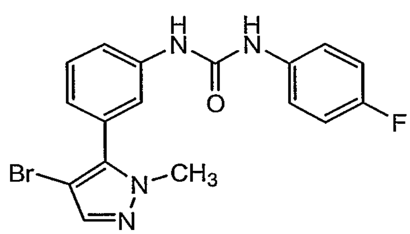

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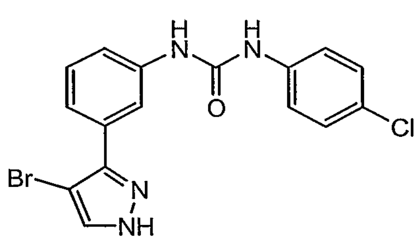

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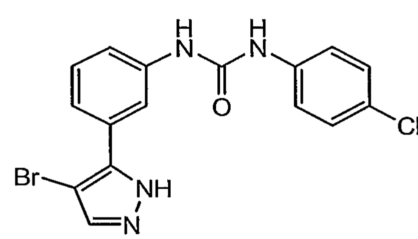
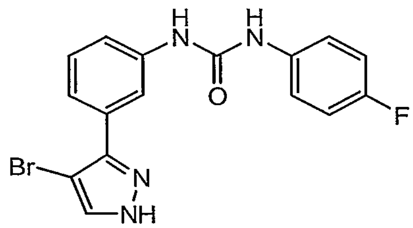
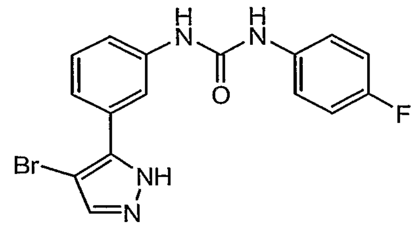
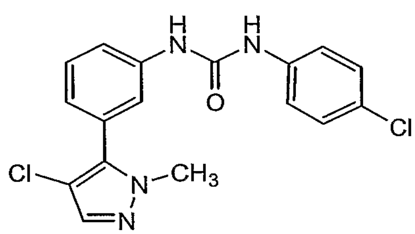


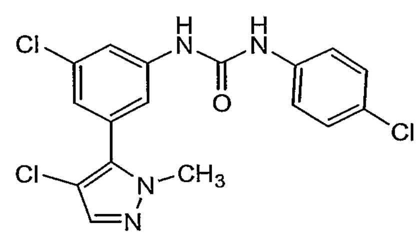
 and 

[0253] Also provided by the present invention are compositions comprising each of the compounds of the invention.

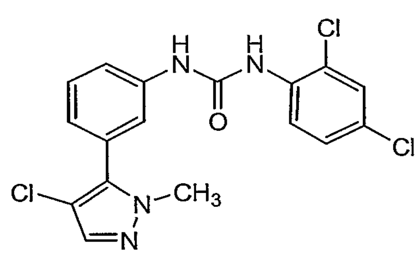
[0254] Other preferred compounds provided by the present invention and useful in the methods disclosed herein, include, but are not limited to:



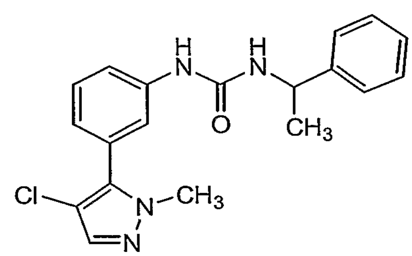
Compound **48**



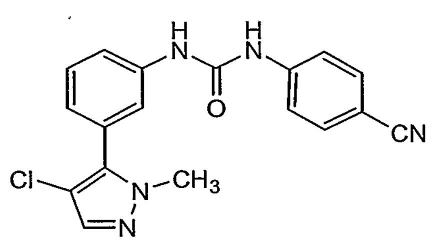
Compound **49**



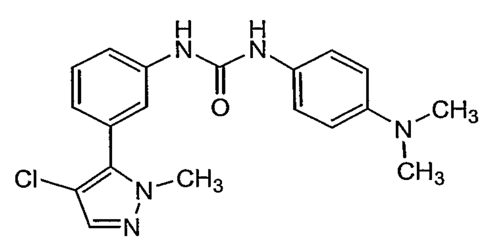
Compound **50**



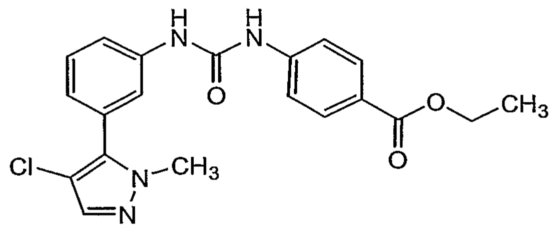
Compound **51**



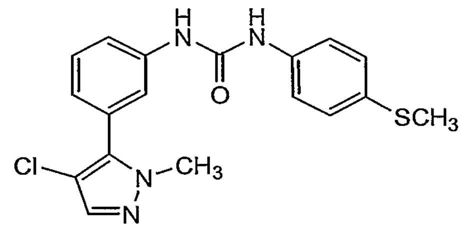
Compound **52**



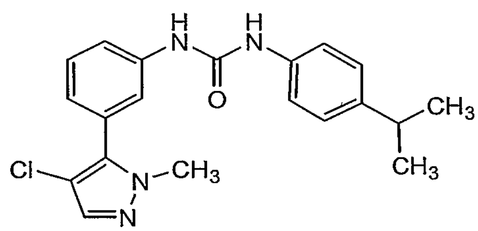
Compound **53**



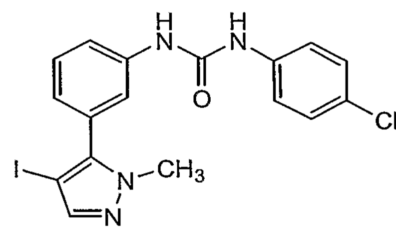
Compound **54**



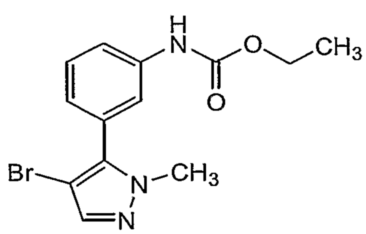
Compound **55**



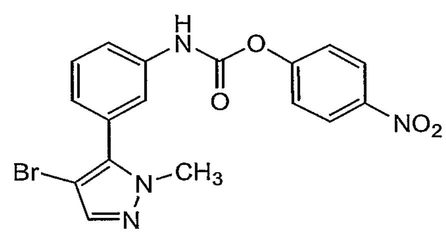
Compound **56**



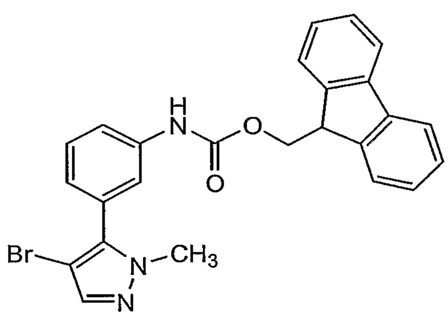
Compound **57**



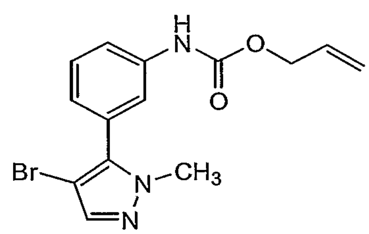
Compound **58**



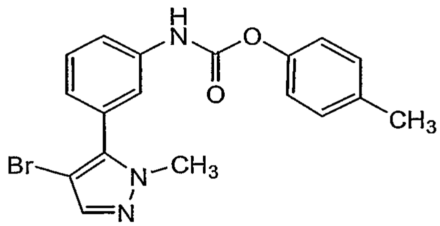
Compound **59**



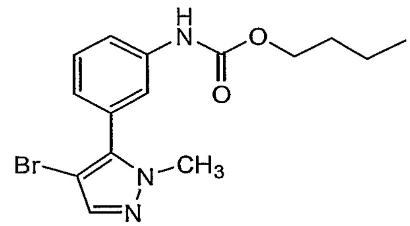
Compound **60**



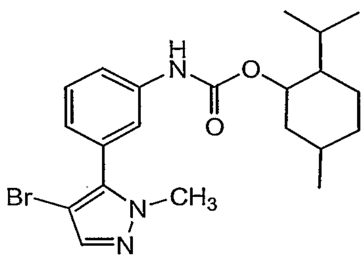
Compound **61**



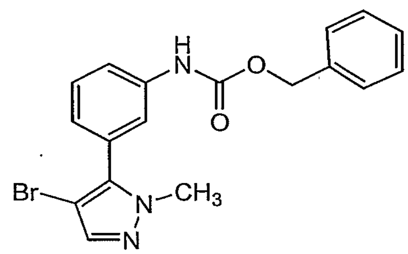
Compound **62**



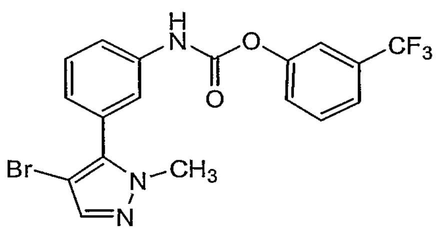
Compound **63**



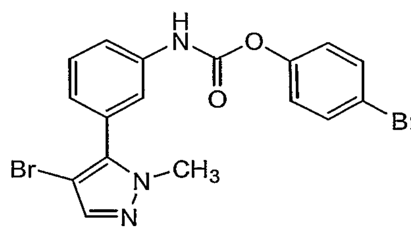
Compound **64**



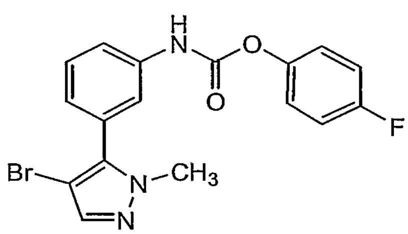
Compound **65**



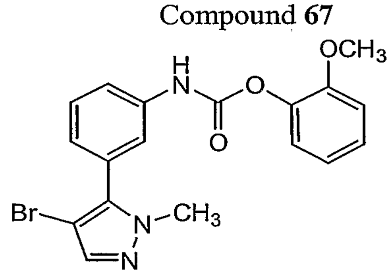
Compound **66**



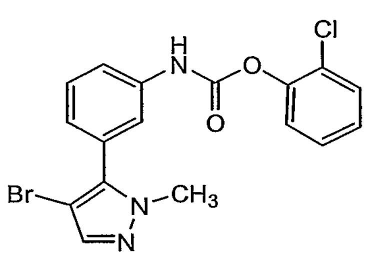
Compound **67**



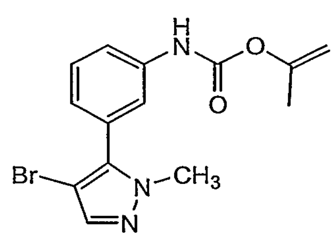
Compound **68**



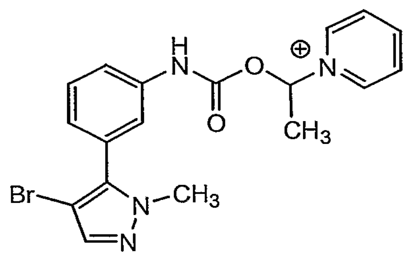
Compound **69**



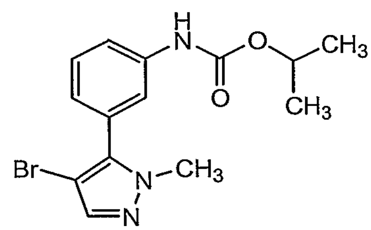
Compound **70**



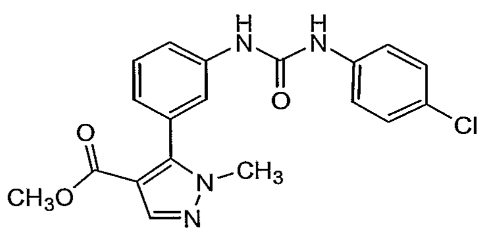
Compound **71**



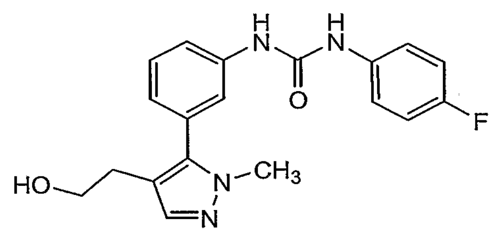
Compound **72**



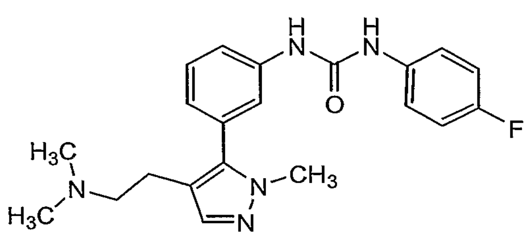
Compound **73**



Compound **74**



Compound **75**



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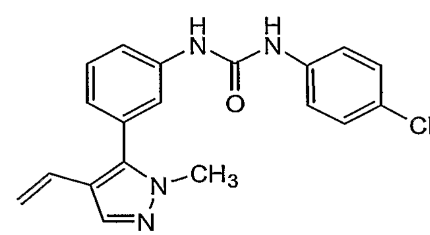

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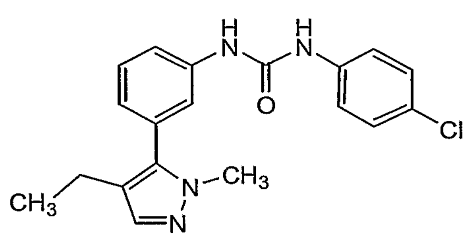

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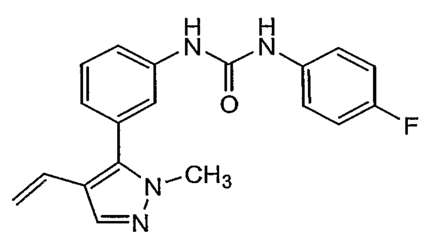

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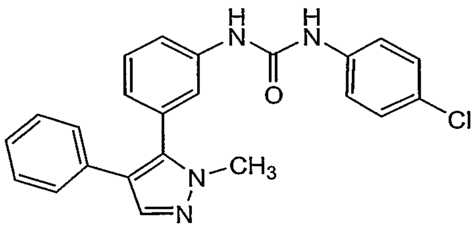

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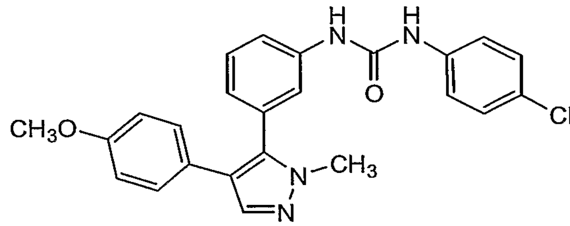

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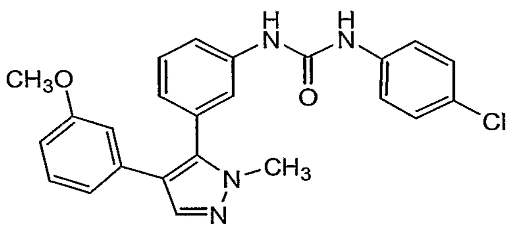

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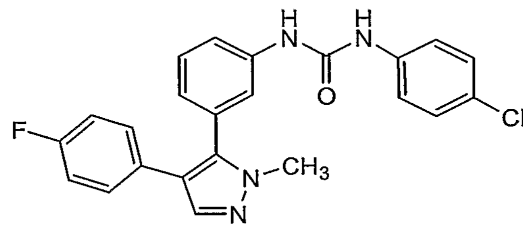

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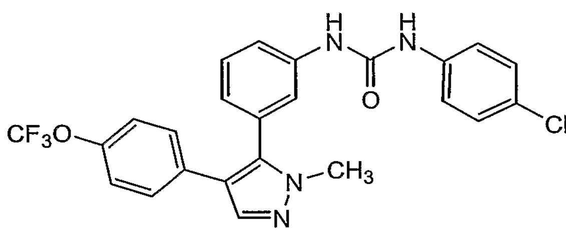

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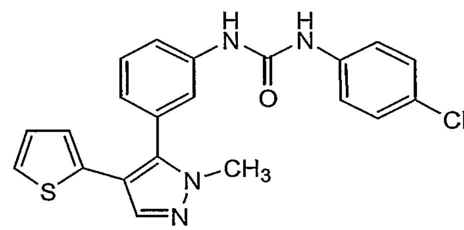

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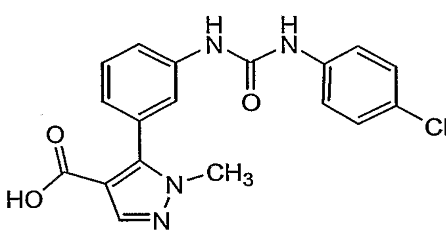

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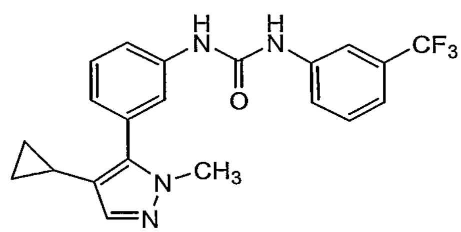

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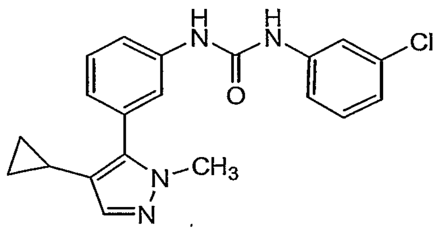

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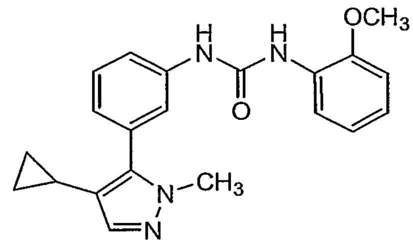

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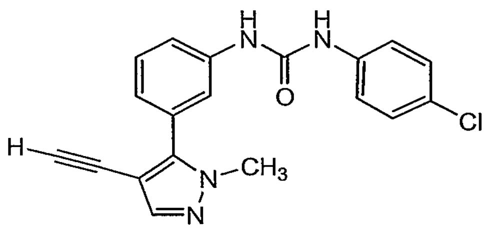

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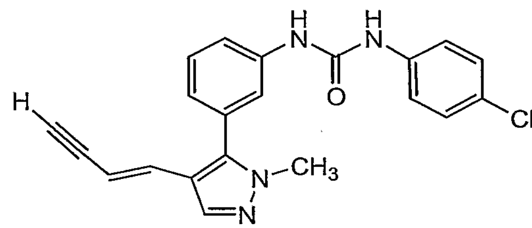

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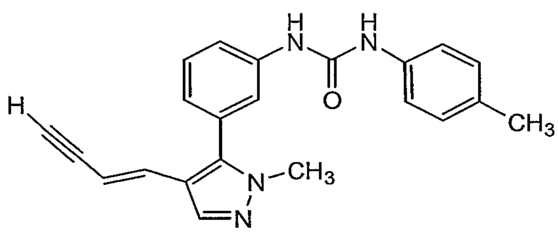

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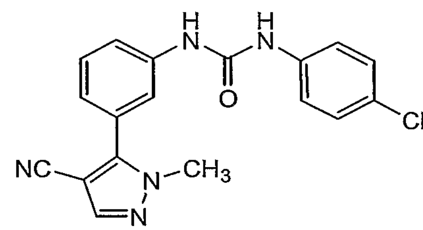

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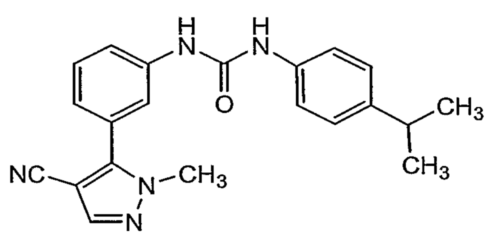

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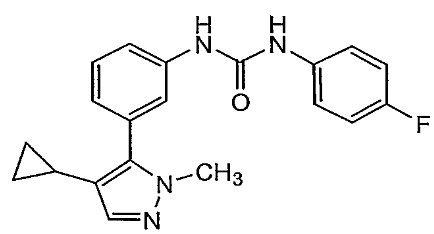

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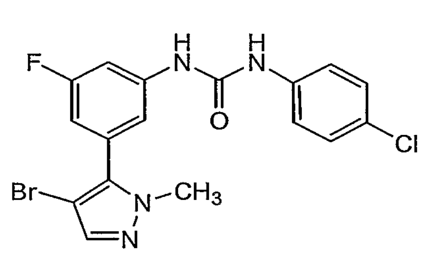

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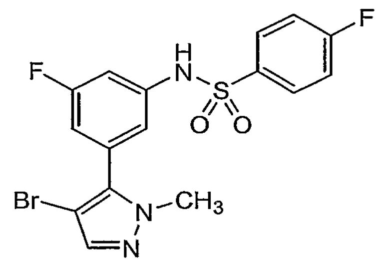

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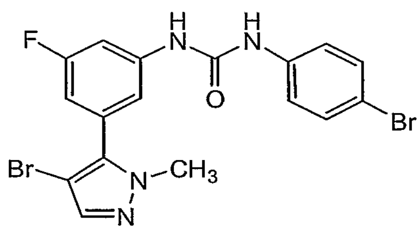

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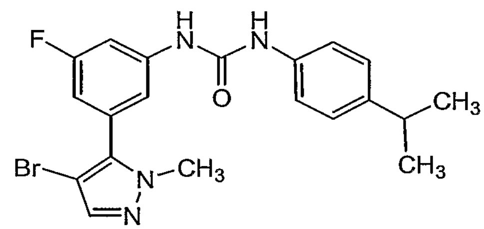

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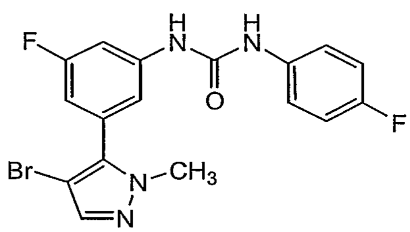

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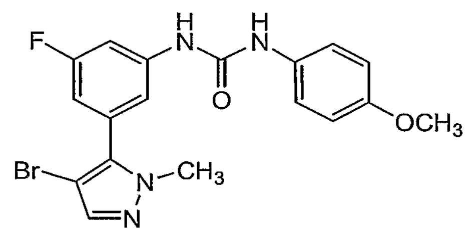

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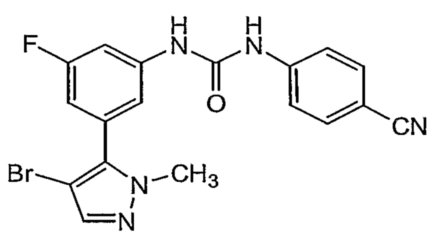

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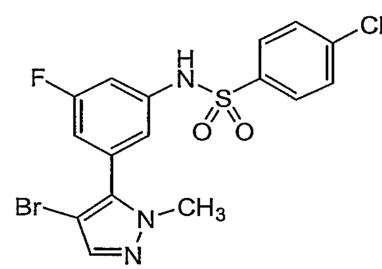

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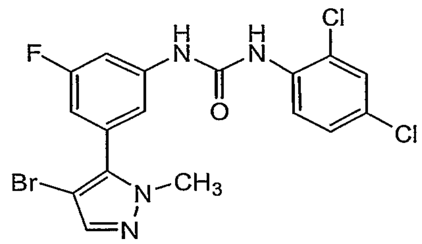

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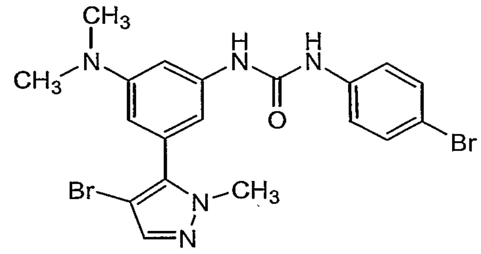

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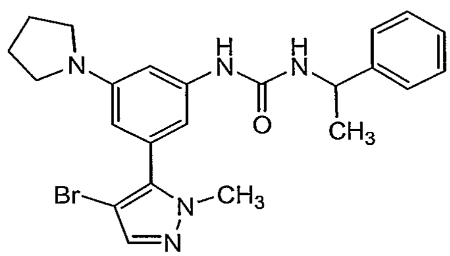

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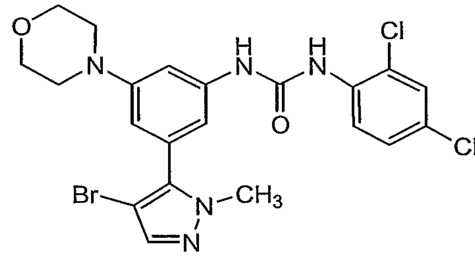

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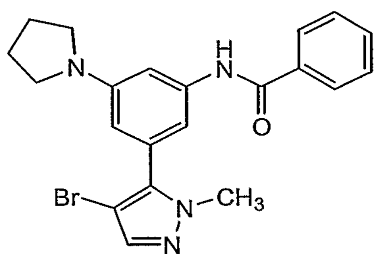

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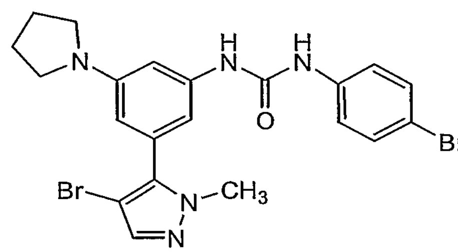

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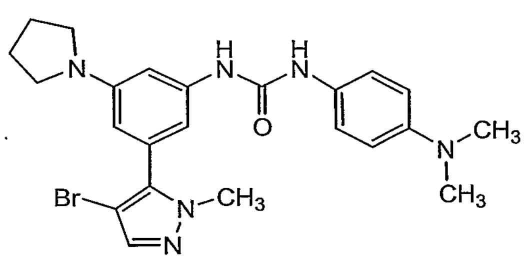

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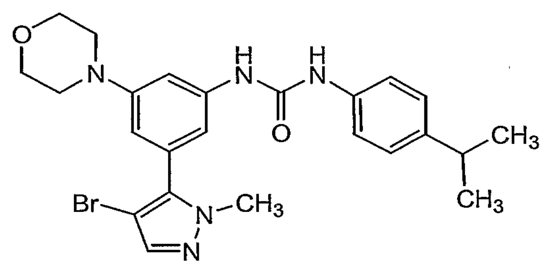

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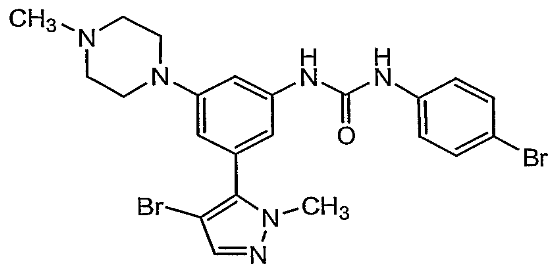

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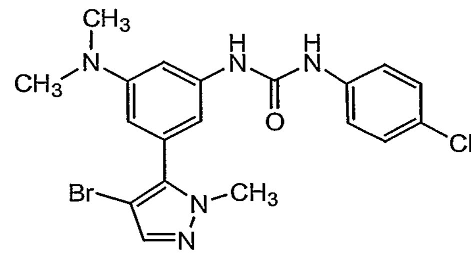

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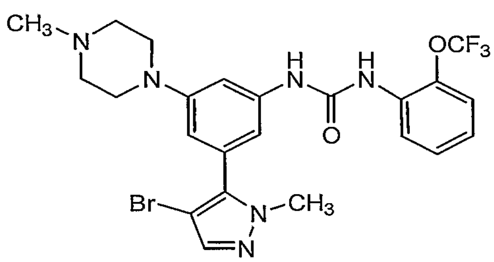

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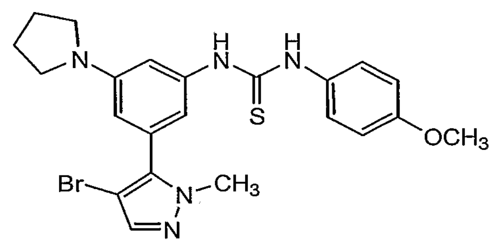

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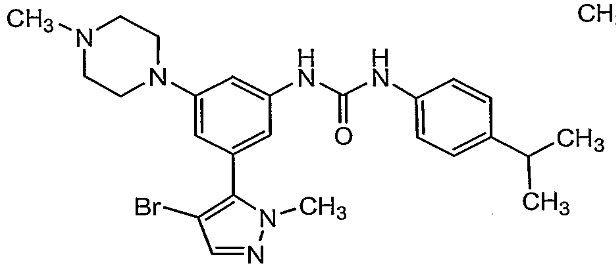

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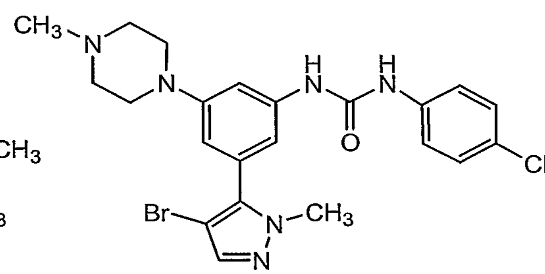

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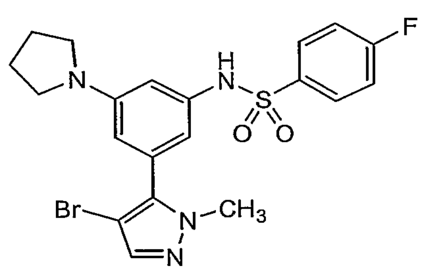

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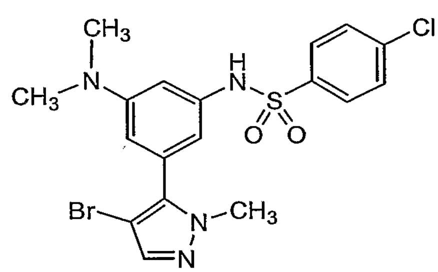

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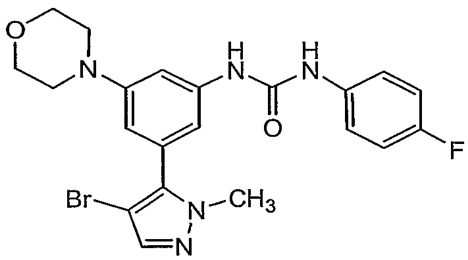

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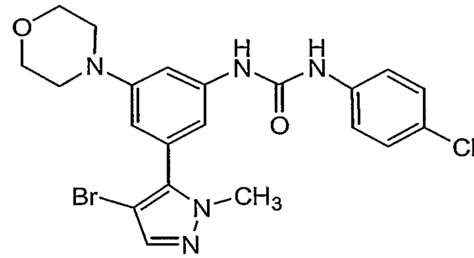

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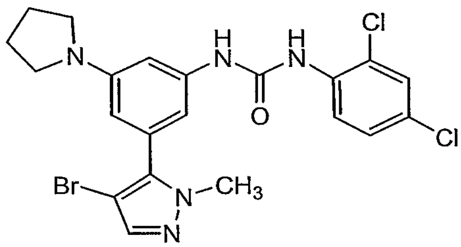

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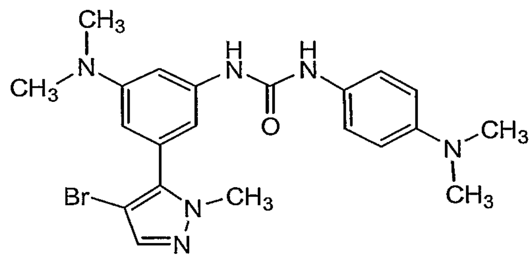

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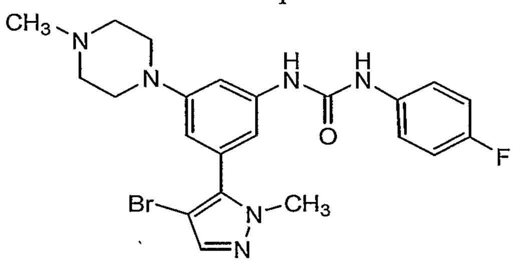

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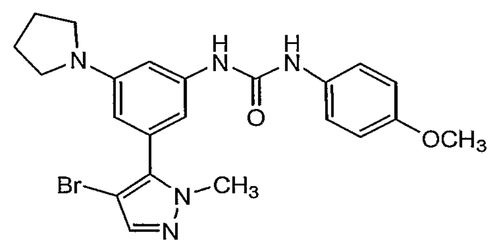

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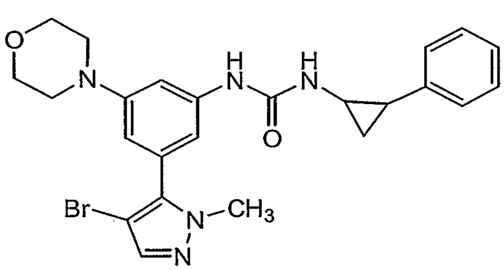

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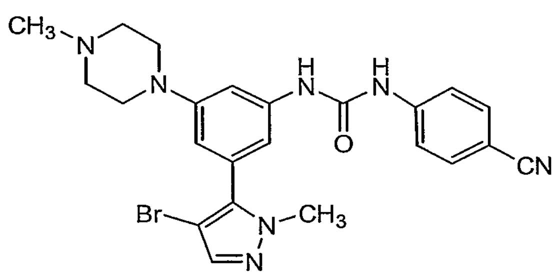

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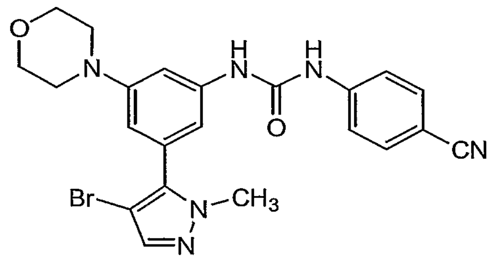

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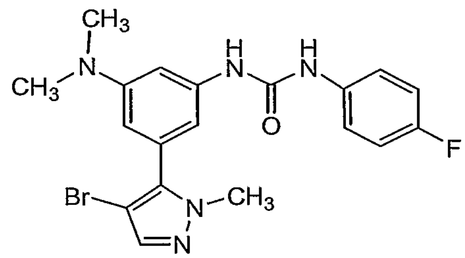

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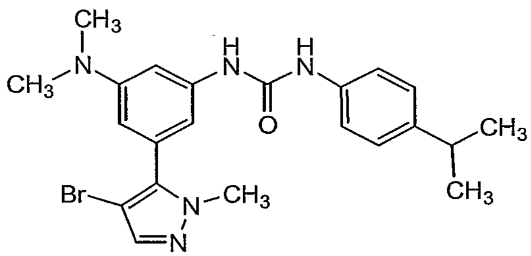

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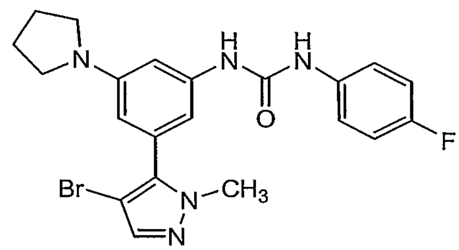

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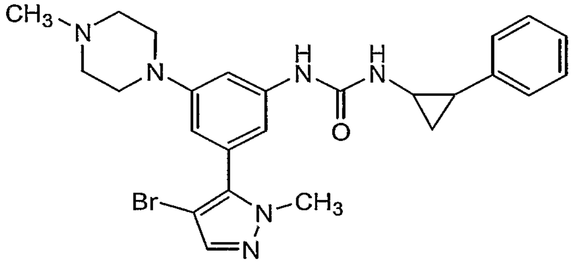

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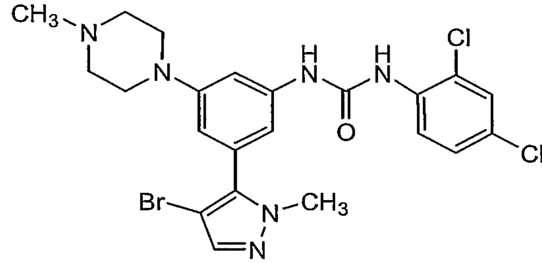

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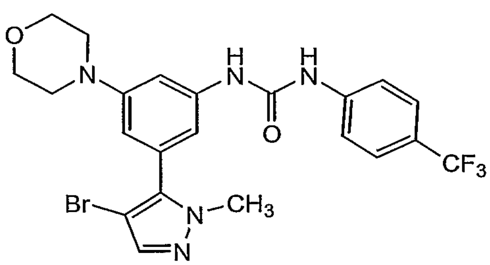

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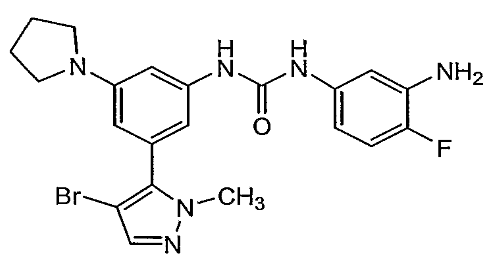

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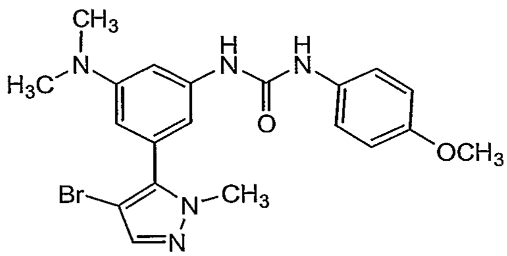

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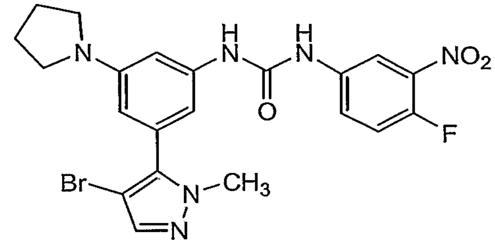

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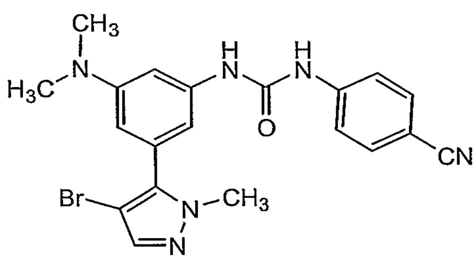

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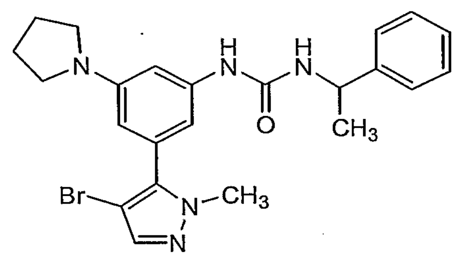

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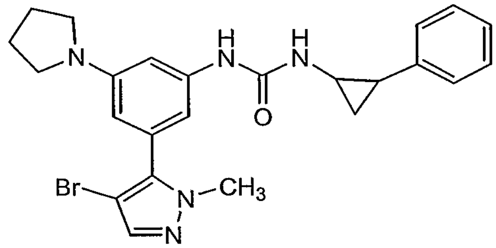

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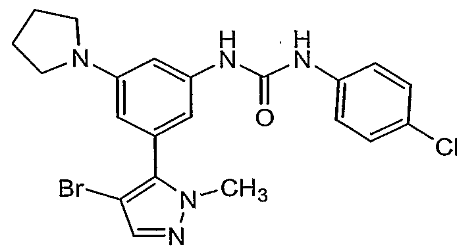

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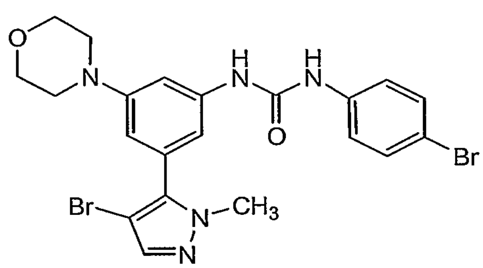

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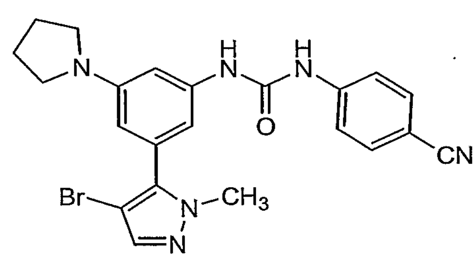

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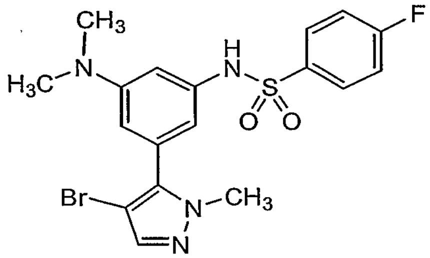

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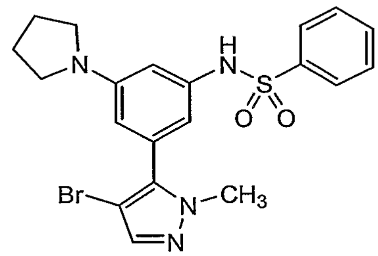

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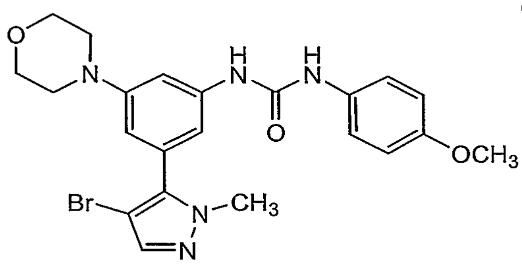

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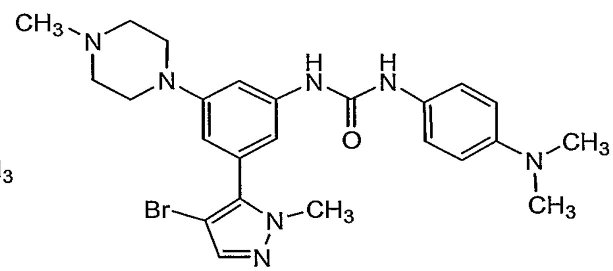
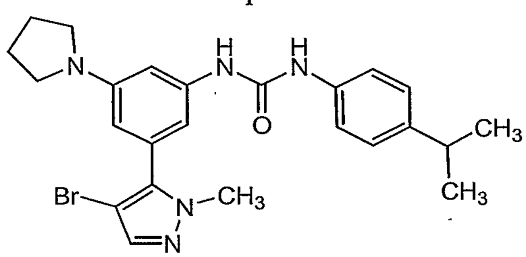
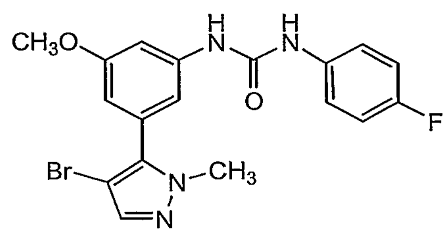


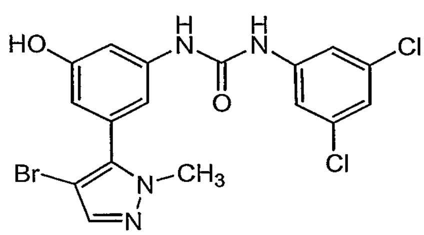
Compound **147**



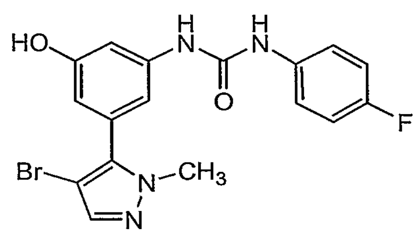
Compound **148**



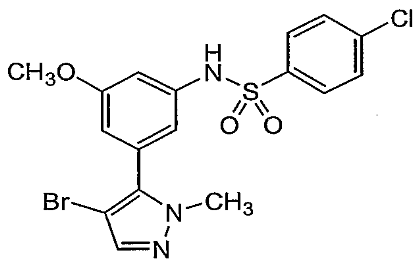
Compound **149**



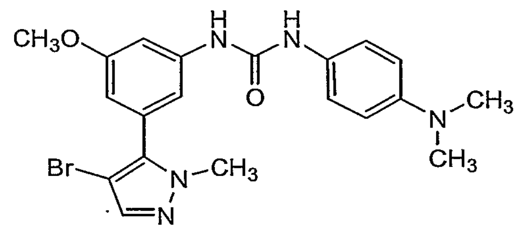
Compound **150**



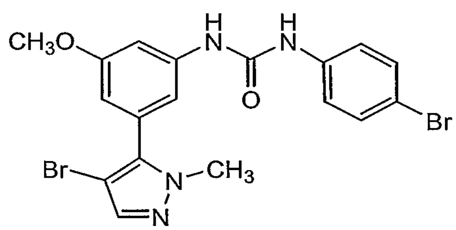
Compound **151**



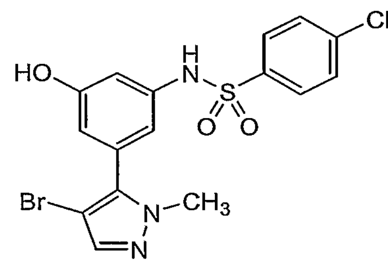
Compound **152**



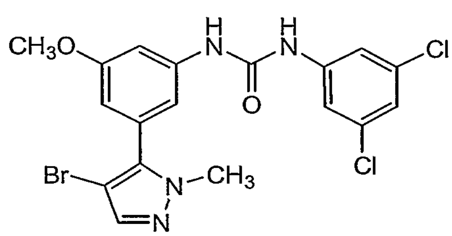
Compound **153**



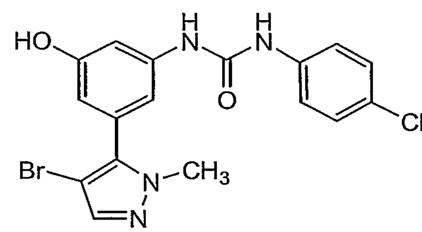
Compound **154**



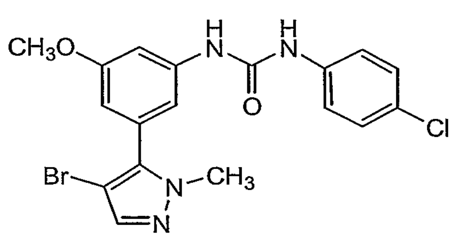
Compound **155**



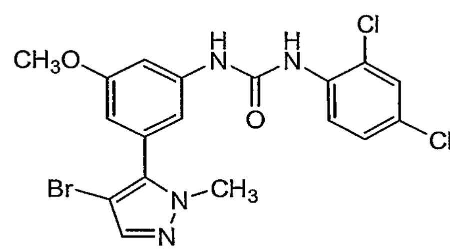
Compound **156**



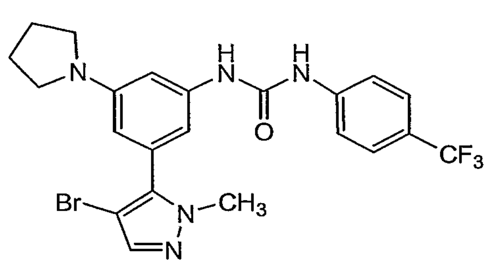
Compound **157**



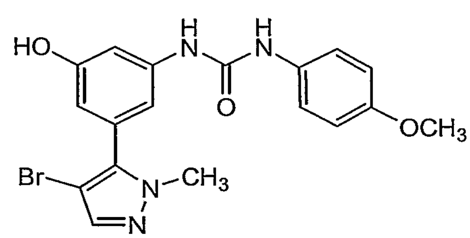
Compound **158**



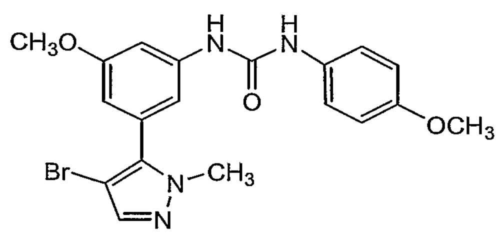
Compound **159**



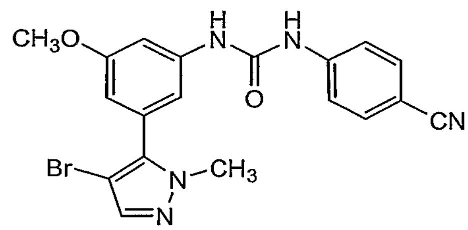
Compound **160**



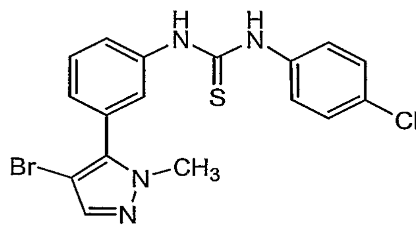
Compound **161**



Compound **162**

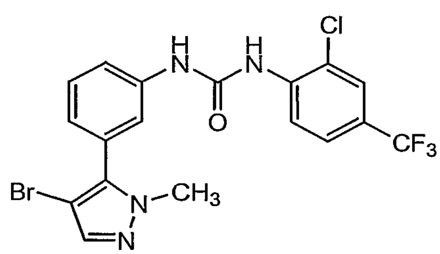


Compound **163**

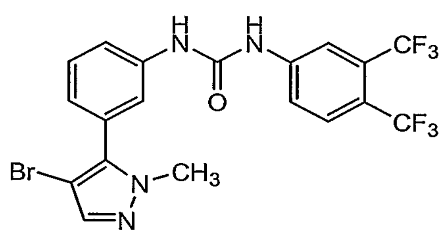


Compound **164**

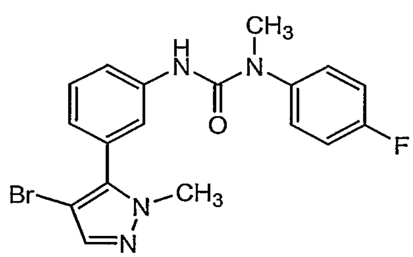
[0255] Other preferred compounds of the present invention include compounds of the following group:



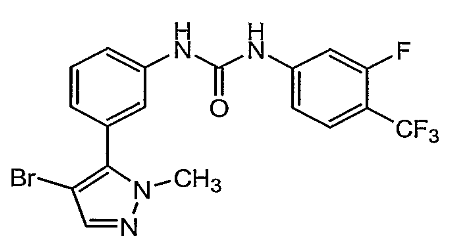
1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-urea



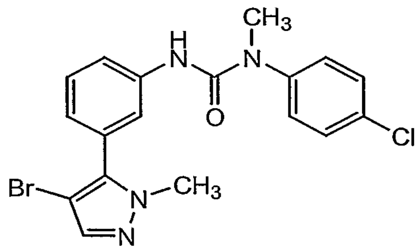
1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-urea



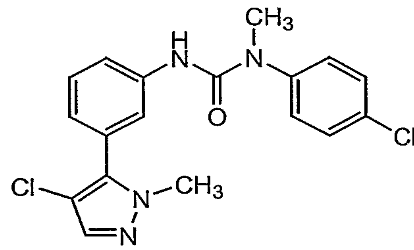
3-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea



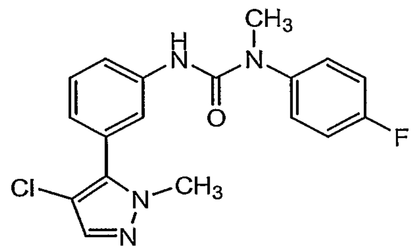
1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-phenyl)-urea



3-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea



3-[3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea

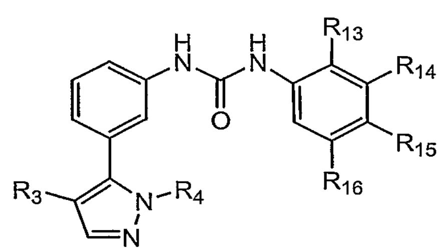


3-[3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea .

[0256] In some embodiments of each of the genera described herein, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0257] In some embodiments of each of the genera described herein, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0258] Still other preferred compounds falling within the scope of the general Formula (**I**) have the Formula LX:



(LX)

wherein:

R_3 is Br or Cl;

R_4 is lower alkyl;

R_{10} is H, F or CF_3;

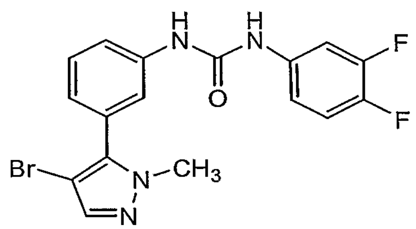
R_{11} is H, F, Cl or CF_3;

R_{12} is H, F or Cl;

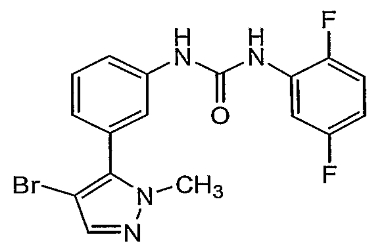
R_{13} is H or F;

and combinations and subcombinations thereof.

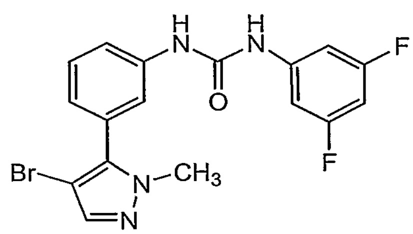
[0259] Specifically preferred compounds of Formula (**LX**) above include the following:



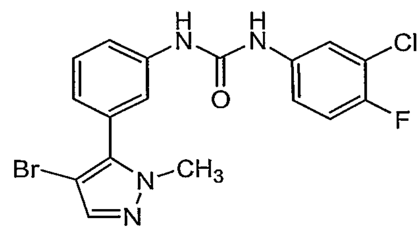
Compound **165**



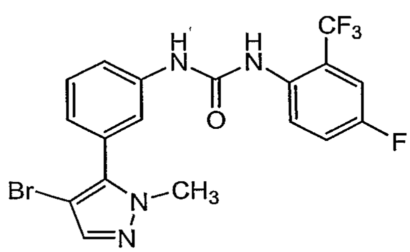
Compound **166**



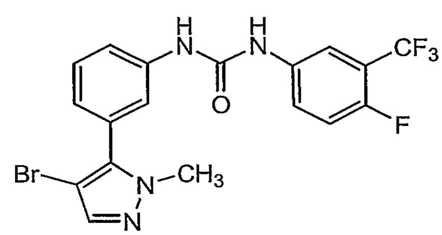
Compound **167**



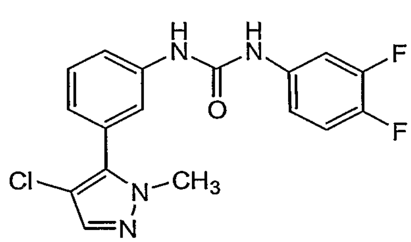
Compound **168**



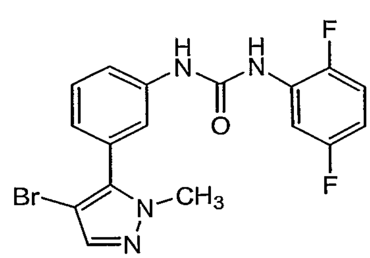
Compound **169**



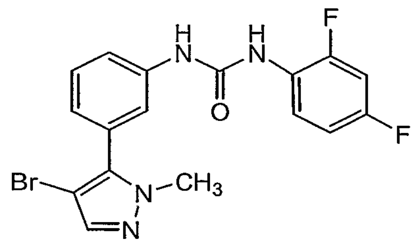
Compound **170**

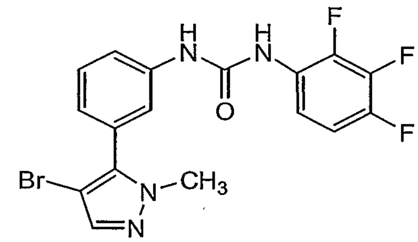


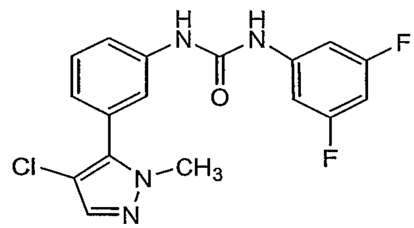
Compound **171**

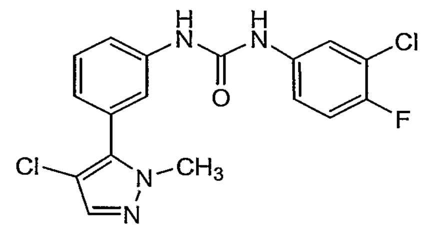


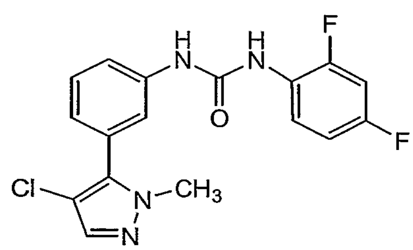
Compound **172**

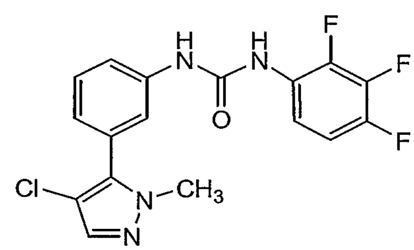

Compound **173**

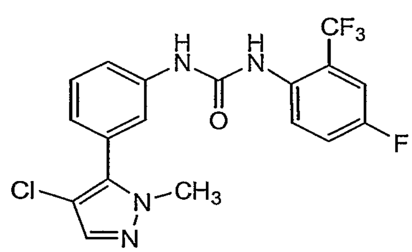

Compound **174**

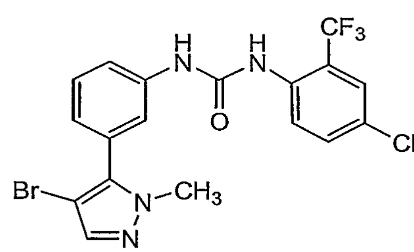

Compound **175**

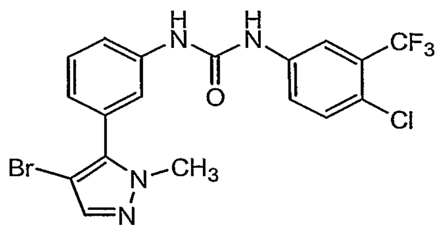

Compound **176**


Compound **177**

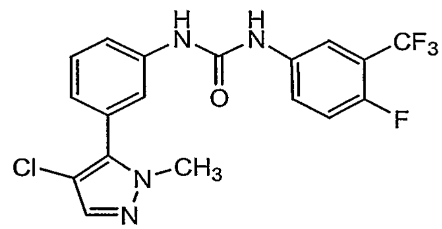

Compound **178**


Compound **179**


Compound **180**



Compound **181**



Compound **182**

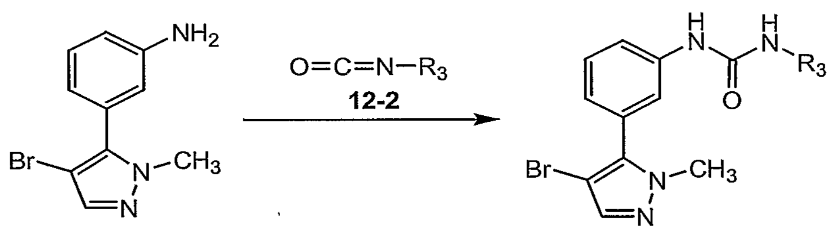
[0260] The IC_{50} values for Compounds **165-182** ranged between 8 to 158 nM in the IP_3 AP-3 assay with their corresponding values shown below:

Compound No.	5-HT_{2A} IC_{50} (nM)
165	27
166	33
167	79
168	17
169	69
170	11
171	17
172	36
173	14
174	18
175	46
176	23
177	24
178	48
179	158
180	34
181	27
182	45

EXAMPLE 12
GENERAL SYNTHETIC APPROACHES

[0261] The compounds disclosed in this invention may be readily prepared in accordance to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art.

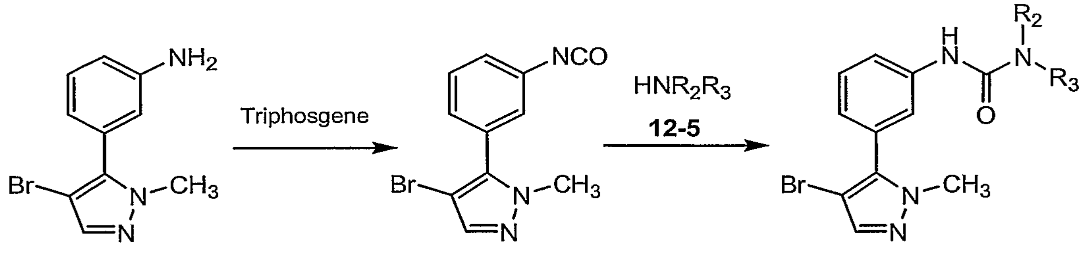
[0262] Compounds of general Formula (I) can be obtained *via* a variety of synthetic routes all of which would be familiar to one skilled in the art. The reaction of isocyanates with amines is a commonly practiced method for the formation of ureas (see Org. Syn. Coll. Vol. V, (1973), 555). Amine **12-1**, 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine (sold commercially as 3-(4-bromo-1-methylpyrazole-3-yl)phenylamine, by Maybridge Chemical Company, Catalog No. KM01978, CAS No. 175201-77-1) reacts readily with isocyanates **12-2** in inert solvents such as halocarbons to yield the desired ureas of Formula **12-3** as shown in Scheme **12-1**.



12-1 **12-3**

Scheme **12-1**

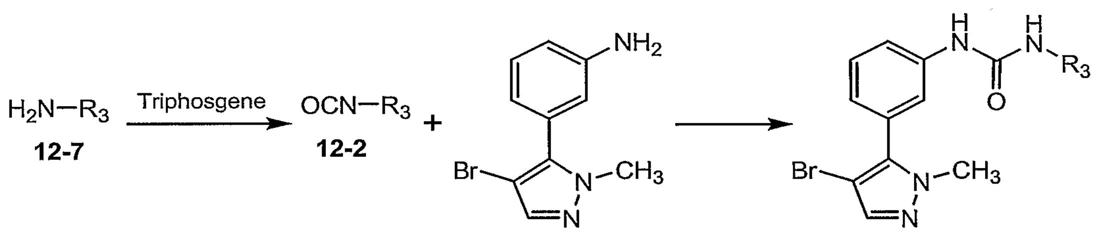
[0263] Alternatively the amine **12-1** can be converted to the corresponding isocyanate **12-4** by the action of phosgene or a suitable phosgene equivalent, *e.g.* triphosgene, in an inert solvent such as a halocarbon in the presence of an organic base such as triethylamine (i.e., TEA) or diisopropylethylamine (i.e., DIEA). Isocyanate **12-4** reacts with amines of the general formula **12-5** in an analogous fashion to that described above in Scheme **12-1** to give urea **12-6**. This approach allows for diverse groups to be introduced for the R_2 or R_3 group based on the starting amine **12-5** (Scheme **12-2**).



12-1 **12-4** **12-6**

Scheme **12-2**

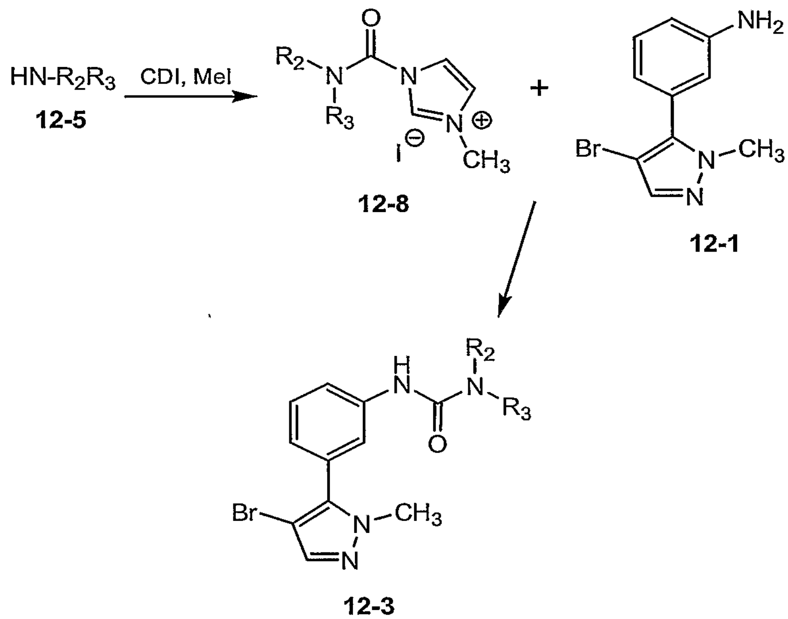
[0264] Alternatively wherein the isocyanate of general formula **12-2** is not commercially available it can be prepared from the corresponding amine of general formula **12-7** in an analogous procedure to that described above for the preparation of **12-1**. Reaction of these isocyanates with **12-1** would again yield the requisite ureas of general formula **12-3** (Scheme **12-3**).



12-1 **12-3**

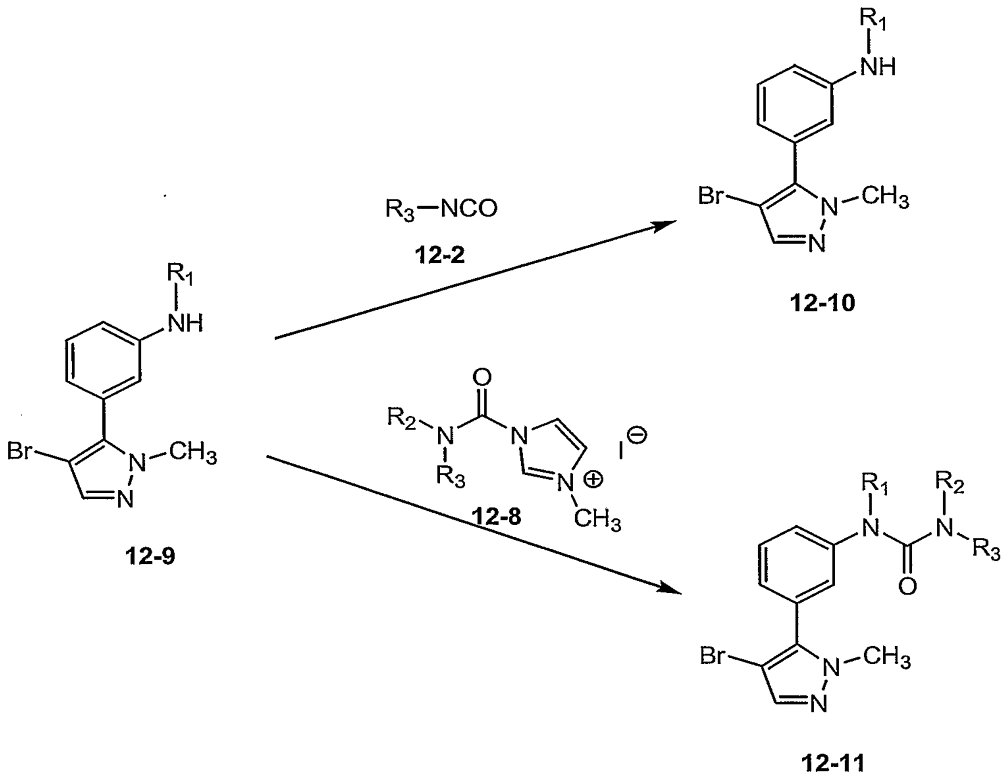
Scheme **12-3**

[0265] Amines of general formula **12-5** are also readily converted to activated isocyanate equivalents of general formula **12-8** by the sequential action of carbonyldiimidazole and methyl iodide in tetrahydrofuran and acetonitrile respectively (R.A. Batey *et al*, *Tetrahedron Lett.*, (1998), 39, 6267-6270.) Reaction of **12-8** with amine **12-1** in an inert solvent such as a halocarbon would yield the requisite ureas of general formula **12-3** (Scheme **12-4**).



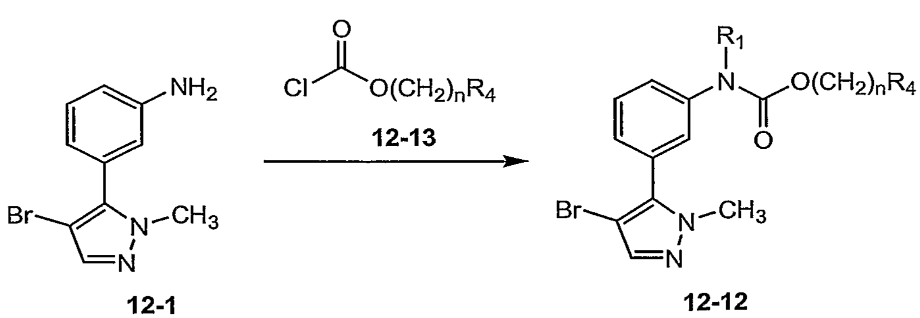
Scheme **12-4**

[0266] Amine **12-1** may be monomethylated according to the procedure of J. Barluenga *et al*, *J. Chem. Soc., Chem. Commun.*, (1984), 20, 1334-1335, or alkylated according to the procedure of P. Marchini *et al*, *J. Org. Chem.*, (1975), 40(23), 3453-3456, to yield compounds of general formula **12-9** wherein R^1 = lower alkyl. Substituted amine **12-9** may be allowed to react with an isocyanate equivalent, either **12-2** or **12-8**, in a similar manner as described herein to give urea **12-10** or **12-11** respectively (Scheme **12-5**).



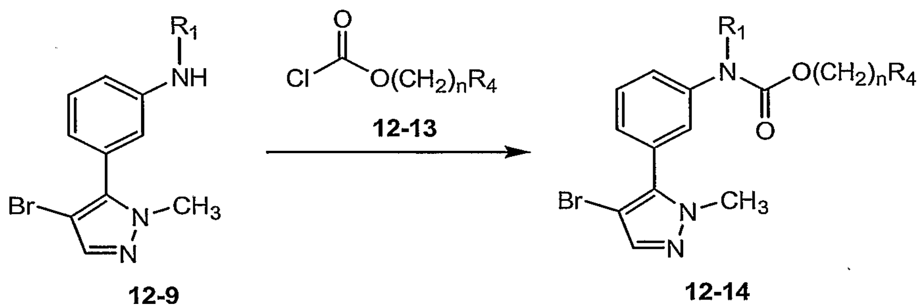
Scheme **12-5**

[0267] Carbamates of general formula **12-12** can be obtained in a similar manner via a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. The reaction of amine **12-1** with chloroformates (see Org. Syn. Coll. Vol. IV, (1963), 780) of general formula **12-13** in an inert solvent such as ether or halocarbon in the presence of a tertiary base such as triethylamine or ethylisopropylamine readily yields the requisite carbamates of general formula **12-12** (Scheme **12-6**).



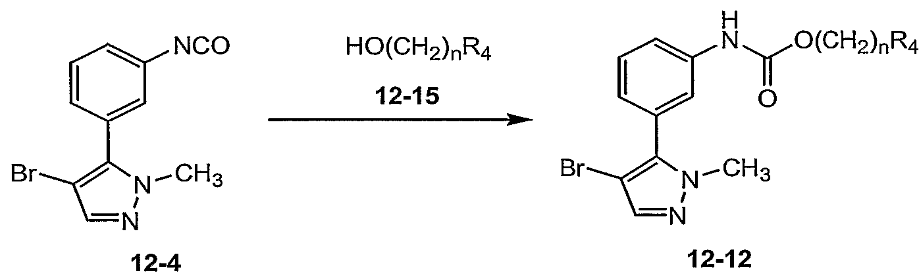
Scheme **12-6**

[0268] Analogously, amines of general formula **12-9** react similarly with chloroformates **12-13** to yield the requisite carbamates of the general formula **12-14** (Scheme **12-7**).



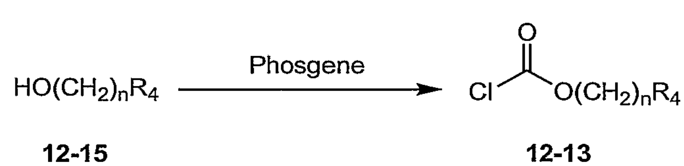
Scheme **12-7**

[0269] An alternate route employs the ready reaction of an alcohol with an isocyanate. Thus isocyanate **12-4** described previously reacts readily with alcohols **12-15** in an aprotic solvent such as ether or chlorocarbon to yield the desired carbamates of general formula **12-12** (Scheme **12-8**). :



Scheme **12-8**

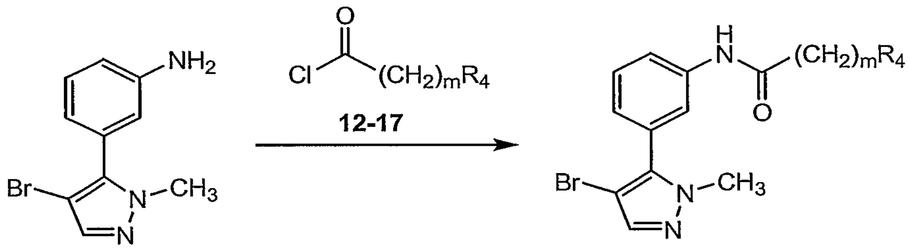
[0270] Chloroformates of general formula **12-13** not commercially available may be readily prepared from the corresponding alcohol **12-15** in an inert solvent such as toluene, chlorocarbon or ether by the action of excess phosgene (see Org. Syn. Coll. Vol. III, (1955), 167) (Scheme **12-9**).



Scheme **12-9**

[0271] Amide compounds of the general formula **12-16** can be obtained via a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. The reaction of amine

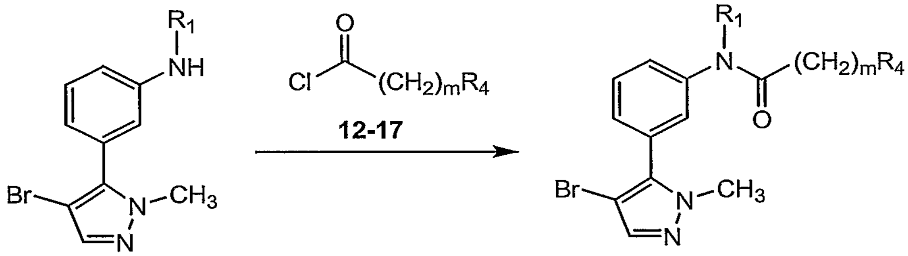
12-1 with acid chlorides (see Org. Syn. Coll. V, (1973), 336) of general formula **12-17** to yield the desired amides **12-16** is readily achieved in an inert solvent such as chloroform or dichloromethane in the presence of an organic base such as triethylamine or ethyldiisopropylamine (Scheme **12-10**).



12-1 **12-16**

Scheme **12-10**

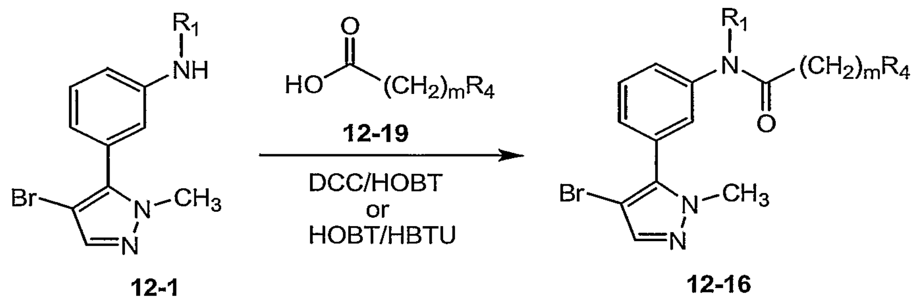
[0272] In an identical fashion amines of general formula **12-9** would react with acid chlorides **12-17** to yield the desired amides **12-18** (Scheme **12-11**).



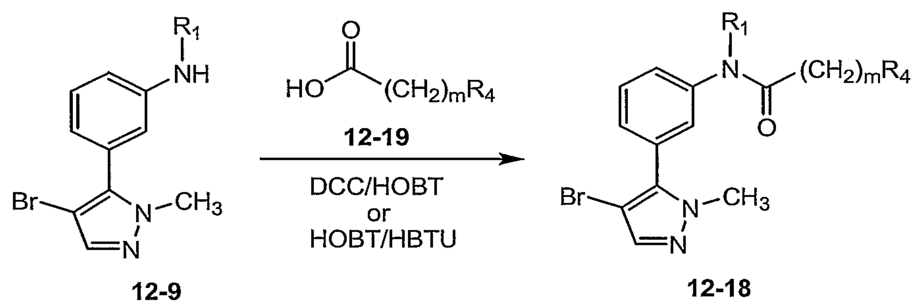
12-9 **12-18**

Scheme **12-11**

[0273] Alternatively the corresponding acids of general formula **12-19** may be coupled with dicyclohexylcarbodiimide (DCC)/hydroxybenzotriazole (HOBT) (see W. Konig et al, Chem. Ber., (1970), 103, 788) or hydroxybenzotriazole (HOBT)/2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (see M. Bernatowicz et al., Tetrahedron Lett., (1989), 30, 4645) as condensing agents in dimethylformamide or chloroform with amines **12-1** and **12-9** respectively to give amides **12-16** (Schemes **12-12**) and **12-18** (Scheme **12-13**) respectively as described above.

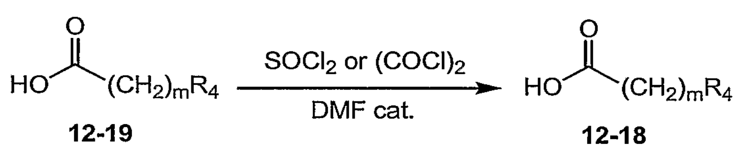


Scheme **12-12**



Scheme **12-13**

[0274] The acids of general formula **12-18** are readily converted to the corresponding acid chlorides **12-19** by the action of thionyl chloride or oxalyl chloride in the presence of catalytic dimethylformamide:



Scheme **12-14**

[0275] A third aspect of the present invention provides a compound of Formula **(I)** or a solvate or physiologically functional derivative thereof for use as a therapeutic agent, specifically as a modifier of the activity of the serotonin 5-HT_{2A} receptor. Modifiers of the activity of the serotonin 5-HT_{2A} receptor are believed to be of potential use for the treatment or prophylaxis of CNS, gastrointestinal, cardiovascular, and inflammatory disorders. Compounds of the Formula **(I)** may be administered by oral, sublingual, parenteral, rectal, or topical administration. In addition to the neutral

forms of compounds of Formula (I) by appropriate addition of an ionizable substituent, which does not alter the receptor specificity of the compound, physiologically acceptable salts of the compounds may also be formed and used as therapeutic agents. Different amounts of the compounds of Formula (I) will be required to achieve the desired biological effect. The amount will depend on factors such as the specific compound, the use for which it is intended, the means of administration, and the condition of the treated individual. A typical dose may be expected to fall in the range of 0.001 to 200 mg per kilogram of body weight of the treated individual. Unit does may contain from 1 to 200 mg of the compounds of Formula (I) and may be administered one or more times a day, individually or in multiples. In the case of the salt or solvate of a compound of Formulas (I), the dose is based on the cation (for salts) or the unsolvated compound.

[0276] A fourth aspect of the present invention provides pharmaceutical compositions, comprising at least one compound of Formula (I) and/or an acceptable salt or solvate thereof (*e.g.*, a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (*e.g.*, pharmaceutical carrier or excipient). Pharmaceutical compositions may be used in the treatment of clinical conditions for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated, particularly where the active ingredient is preferentially selective for the 5-HT_{2A} receptor over the 5-HT_{2A} receptor, and most particularly where the active ingredient is also an inverse agonist at the 5-HT_{2A} receptor. At least one compound of Formula (I) may be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients may be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

[0277] Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tabletting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing

the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

[0278] The fifth aspect of the present invention provides for the use of a compound of formula (I) in the preparation of a medicament for the treatment of a medical condition for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated.

[0279] The sixth aspect of the present invention provides for a method of treatment of a clinical condition of a mammal, such as a human, for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated, which comprises the administration to the mammal of a therapeutically effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

EXPERIMENTAL DATA

EXAMPLE 13

Preparation and Analysis of Compounds

Experiments 13.1 – 13.43

[0280] Mass spectra were recorded on a Micromass Platform™ LC with Gilson HPLC. Infra-red spectra were recorded on a Nicolet Avatar™ 360 FT-IR. Melting points were recorded on a Electrothermal IA9200™ apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Bruker™ 300MHz machine. Chemical shifts are given with respect to tetramethylsilane. In the text the following abbreviations are used; s (singlet), d (doublet), t (triplet), m (multiplet) or combinations thereof. Chemical shifts are quoted in parts per million (ppm) and with coupling constants in Hertz.

[0281] Thin layer chromatography was carried out using aluminium backed silica plates (250μL; GF_{254}). HPLC was recorded either on a HP Chemstation™ 1100 HPLC using a Hichrom 3.5 C18 reverse phase column (50mm x 2.1mm i.d.). Linear gradient elution over 5 minutes – 95% water (+0.1% TFA) / 5% acetonitrile (+0.05% TFA) down to 5% water / 95% acetonitrile. Flow rate 0.8mL/min (Method A); or on a Hichrom 3.5 C18 reverse phase column (100mm x 3.2mm i.d.). Linear gradient elution over 11 minutes – 95% water (+0.1% TFA) / 5% acetonitrile (+0.05% TFA) down to 5% water / 95% acetonitrile. Flow rate 1mL/min (Method B). Samples were routinely monitored at 254nM unless otherwise stated.

[0282] All reagents were purchased from commercial sources.

Experiment 13.1

Preparation and Analysis of Compound 1

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide

[0283] To 4-methoxyphenylchloroformate (19 mg, 0.10 mmol) in CH2Cl2 (0.5 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (25 mg, 0.10 mmol) and triethylamine (14 μL, 0.10 mmol) in CH2Cl2 (0.5 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica (40% EtOAc/hexane) gave the title compound as a colourless solid (21 mg, 52%), m.p. 140.3-141.8oC. (EtOAc/hexane).

IR: v_{max} =1748, 1592, 1504, 1412, 1190, 835, 764, 676 $cm.^{-1}$ MS (ES+): m/z (%)=404 (M+H ^{81}Br, 100), 402 (M+H ^{79}Br, 90).

^1H-NMR (CD_3 OD): δ =3.80 (3H, s, CH_3), 3.81 (3H, s, CH_3), 6.91-6.98 (2H, m, ArH), 7.07-7.18 (3H, m, ArH), 7.42-7.53 (4H, m, ArH).

[0284] HPLC: retention time 3.28 mins (Method A). Tlc: Rf 0.4 (EtOAc/hexane).

Experiment 13.2

Preparation and Analysis of Compound 2

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide

[0285] To thiophene-2-carbonyl chloride (11 μL, 0.09 mmol) in CH2Cl2 (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (25 mg, 0.09 mmol) and triethylamine (14 μL, 0.09 mmol) in CH2Cl2 (0.5 mL). The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (24 mg, 68%), m.p. 127.8-128.6°C (EtOAc/hexane). :

MS (ES+): m/z (%)=364 (M+H ^{81}Br, 96), 362 (M+H ^{79}Br, 100).

^1H-NMR (CD_3 OD): δ =3.81 (3H, s, CH_3), 7.19 (2H, m, ArH), 7.48-7.58 (2H, m, ArH), 7.68-7.83 (3H, m, ArH), 7.93 (1H, dd, J=1.0, 3.8, ArH).

[0286] HPLC: retention time 3.12 min (Method A). TLC: Rf 0.30 (30% EtOAc/hexane).

Experiment 13.3

Preparation and Analysis of Compound 7

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl) amino)carboxamide

[0287] This compound is commercially available from Maybridge Chemical Company, Catalog No. KM04515, under the name N-(3-(4-bromo-1-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl) amino)carboxamide. :

Experiment 13.4

Preparation and Analysis of Compound 10

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl)methyl)amino)carboxamide

[0288] To a stirred solution of triphosgene (12 mg, 0.04 mmol) in CH2Cl2 (0.5 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (33 μL, 0.24 mmol) in CH2Cl2 (0.5 mL). After 1 h, 4- (trifluoromethoxy)benzylamine (23 mg, 0.12 mmol) was added. The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (75% EtOAc/hexane) gave the title compound as a colourless solid (38 mg, 68%), m.p. 144.6-145.8 °C (EtOAc/hexane).

IR: . ν_{max} =1626, 1558, 1278, 1160, 969, 871, 789, 703 cm-^{1} MS (ES+): m/z (%)=471 (M+H ^{81}Br, 91), 469 (M+H ^{79}Br, 100).

^{1}H-NMR (CD$_3$ OD): δ =3.81 (3H, s, CH$_3$), 4.42 (2H, s, CH$_2$), 7.06 (1H, d, J=7.1, ArH), 7.24 (2H, d, J=8.4, ArH), 7.37-7.52 (6H, m, ArH).

[0289] HPLC: retention time 3.06 mins (Method A). Tlc: Rf 0.5 (EtOAc).

Experiment 13.5

Preparation and Analysis of Compound 39

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide

[0290] To di-tert-butyl dicarbonate (36 mg, 0.17 mmol) in methanol (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (42 mg, 0.17 mmol) in methanol (1 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica (40% EtOAc/hexane) gave the title compound as a colourless solid (29 mg, 49%) (EtOAc/hexane).

MS (CI-): m/z (%)=352 (M-H ^{81}Br, 100), 350 (M-H ^{79}Br, 96).

^{1}H-NMR (DMSO d_6): δ =1.46 (9H, s, 3.times. CH_3), 3.73 (3H, s, CH_3), 7.07 (1H, m, ArH), 7.42 (1H, t, J=7.7, ArH), 7.53-7.60 (2H, m, ArH), 7.64 (1H, s, ArH), 9.57 (1H, s, NH).

[0291] HPLC: retention time 7.15 min (Method B).

Experiment 13.6

Preparation and Analysis of Compound 40

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl)carboxamide

[0292] To 4-(trifluoromethoxy)benzoyl chloride (19 μL, 0.12 mmol) in CH2Cl2 (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (17 μL, 0.12 mmol) in CH2Cl2 (0.5 mL). The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (40 mg, 76%), m.p. 138.6-139.6°C (EtOAc/hexane).

MS (ES+): m/z (%)=442 (M+H ^{81}Br, 93), 440 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ=3.79 (3H, s, CH_3), 7.27 (1H, m, ArH), 7.45-7.60 (3H, m, ArH), 7.65 (1H, s, ArH), 7.87 (2H, m, ArH), 8.09 (2H, m, ArH), 10.51 (1H, s, NH).

[0293] HPLC: retention time 3.60 min (Method A). TLC: Rf 0.40 (50% EtOAc/hexane).

Experiment 13.7

Preparation and Analysis of Compound 41

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl)carboxamide

[0294] To 4-chlorobenzoyl chloride (15 mg, 0.08 mmol) in CH2Cl2 (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (21 mg, 0.08 mmol) and triethylamine (12 μL, 0.08 mmol) in CH2Cl2 (0.5 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (23 mg, 72%), m.p. 184.4-184.8 °C (EtOAc/hexane).

MS (ES+): m/z (%)=394 (M+H ^{81}Br ^{37}Cl, 34), 392 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 390 (M+H ^{79}Br ^{35}Cl, 67).

^{1}H-NMR (DMSO d_6): δ =3.79 (3H, s, CH_3), 7.25 (1H, d, J=7.9, ArH), 7.51-7.6 (3H, m, ArH), 7.69 (1H, s, ArH), 7.90 (2H, m, ArH), 8.00 (2H, m, ArH), 10.51 (1H, s, NH).

[0295] HPLC: retention time 3.40 min (Method A). TLC: Rf 0.35 (50% EtOAc/hexane).

Experiment 13.8

Preparation and Analysis of Compound 42

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)acetamide

[0296] A solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole(35 mg, 0.14 mmol) and triethylamine (23 μL, 0.17 mmol) in DMF (0.5 mL) was added in one portion to a stirred solution of 4-trifluoromethoxyphenylacetic acid (31 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol) and HOBT (19 mg, 0.14 mmol) in DMF (1 mL). The mixture was heated at 70 °C for 24 h and then quenched with aqueous sodium bicarbonate solution. Ethyl acetate was added and the organic phase separated, washed with water (.times.3), brine, dried (MgSO4) and evaporated.

[0297] Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (43 mg, 68%). m.p. 141.2-142.5 oC (EtOAc/hexane).

IR: v_{max} =1684, 1592, 1510, 1253, 1217, 1157, 987, 798, 700 cm^{-1}.

MS (ES+): m/z (%)=456 (M+H ^{81}Br, 100), 454 (M+H ^{79}Br, 94).

^{1}H-NMR (DMSO d_6): δ =3.72 (2H, s, CH_2), 3.75 (3H, s, CH_3), 7.17 (1H, d, J=7.7, ArH), 7.33 (2H, d, J=8.7, ArH), 7.38-7.51 (3H, m, ArH), 7.62-7.73 (3H, m, ArH), 10.44 (1H, s, NH).

[0298] HPLC: retention time 3.52 min (Method A).

Experiment 13.9

Preparation and Analysis of Compound 43

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl)acetamide

[0299] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 3-fluorophenylacetic acid (18 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (12 mg, 26%). Rf 0.41 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=390 (M-H ^{81}Br 100), 388 (M-H ^{79}Br, 100).

^{1}H-NMR ($CDCl_3$): δ = 3.77 (2H, s), 3.83 (3H, s), 7.02-7.20 (4H, m), 7.54 (1H, s), 7.60-7.63 (1H, m).

[0300] HPLC (Method B): retention time 7.07 min (100%).

Experiment 13.10

Preparation and Analysis of Compound 44

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl)acetamide

[0301] A solution of 3-methoxyphenylacetyl chloride (0.02 ml, 0.12 mmol) in dichloromethane (0.75ml) was added dropwise at 0 °C to a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (0.02 ml, 0.13 mmol) in dichloromethane (0.75 ml). The resulting mixture was stirred at room temperature for 16 h and then poured into brine. The organic layer was washed with more brine then dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (9 mg, 19%). Rf 0.30 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=402 (M+H ^{81}Br, 100), 400 (M+H ^{79}Br, 95).

^{1}H-NMR ($CDCl_3$): δ = 3.76 (2H, s), 3.82 (3H, s), 3.85 (3H, s), 6.84-6.90 (3H, m), 7.07-7.44 (5H, m), 7.53 (1H, s), 7.60 (1H, br s).

[0302] HPLC (Method B): retention time 8.62 min (97.09%). δ_H ($CDCl_3$)

Experiment 13.11

Preparation and Analysis of Compound 45

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl)acetamide

[0303] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 2-fluorophenylacetic acid (18 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (15 mg, 32%). Rf 0.52 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=390 (M+H ^{81}Br, 100), 388 (M+H ^{79}Br, 100).

^{1}H-NMR ($CDCl_3$): δ = 3.79 (2H, s), 3.83 (3H, s), 7.11-7.23 (3H, m), 7.30-7.55 (6H, m), 7.61-7.64 (1H, m).

[0304] HPLC (Method B): retention time 7.28 min (100%).

Experiment 13.12

Preparation and Analysis of Compound 46

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide

[0305] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole(30 mg, 0.12 mmol), 4-nitrophenylacetic acid (22 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (9 mg, 18%). Rf 0.19 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=417 (M+H ^{81}Br, 100), 415 (M+H ^{79}Br, 100).

^{1}H-NMR ($CDCl_3$): δ = 3.83 (3H, s), 3.87 (2H, s), 7.18-7.23 (1H, m), 7.42-7.65 (7H, m), 8.22-8.30 (2H, m).

[0306] HPLC (Method B): retention time 7.22 min (94.30%).

Experiment 13.13

Preparation and Analysis of Compound 47

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl)acetamide

[0307] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole(30 mg, 0.12 mmol), 2-methoxyphenylacetic acid (20 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (chloroform-methanol, 99:1), giving the title compound (18 mg, 38%) as a colourless solid. Rf 0.65 (chloroform-methanol, 98:2).

MS (AP-): m/z (%)=400 (M-H ^{81}Br, 90), 398 (M-H ^{79}Br, 100).

^{1}H-NMR($CDCl_3$) δ =3.76 (2H, s), 3.83 (3H, s), 3.98 (3H, s), 6.97-7.06 (2H, m), 7.11-7.16 (1H, m), 7.31-7.50 (4H, m), 7.53 (1H, s), 7.57-7.60 (1H, m), 7.91 (1H, br s).

[0308] HPLC (Method B): retention time 7.16 min (100%).

[0309] One or the other (as indicated) of the two following synthetic protocols was used to generate each of the compounds below:

Protocol A:

[0310] To an isocyanate (1 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (1 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for 16 hours and concentrated. Chromatography on flash silica (20%-80% EtOAc/hexane) followed by recrystallisation gave the pure urea.

Protocol B:

[0311] To a stirred solution of triphosgene (0.33 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole(1 mmol) and triethylamine (2 mmol) in CH_2Cl_2 (4 mL). After 1 hour, an aniline was added (1 mmol). The reaction mixture was stirred for 16 hours and concentrated. Chromatography on flash silica (20%-80% EtOAc/hexane) followed by recrystallisation gave the pure urea. :

Experiment 13.14

Preparation and Analysis of Compound 11

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino)carboxamide

[0312] (Protocol A) – 4-(methylthio)phenyl isocyanate;
colorless solid (EtOAc/hexane).
MS (ES+): m/z (%) = 419 (M+H ^{81}Br, 100), 417 (M+H ^{79}Br, 94).
^{1}H-NMR (MeOH d_4): d = 2.42 (3H, s, SCH3), 3.81 (3H, s, NCH3), 7.06 (1H, m, ArH), 7.22 (2H, m, ArH), 7.37 (2H, m, ArH), 7.42-7.61 (4H, m, ArH).

[0313] HPLC: retention time 3.35 min (Method A).

Experiment 13.15

Preparation and Analysis of Compound 8

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino)carboxamide

[0314] (Protocol A) – 4-chlorophenyl isocyanate;
colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 409 (M+H ^{81}Br ^{37}Cl, 19), 407 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 405 (M+H ^{79}Br ^{35}Cl, 81).

^{1}H-NMR (MeOH d4): d = 3.81 (3H, s, CH_3), 7.07 (^{1}H, m, ArH), 7.23 (2H, m, ArH), 7.36-7.60 (6H, m, ArH).

[0315] HPLC: retention time 3.42 min (Method A).

Experiment 13.16

Preparation and Analysis of Compound 9

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl)carboxamide

[0316] (Protocol A) – 4-fluorophenyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 391 (M+H ^{81}Br, 96), 389 (M+H ^{79}Br, 100).

^{1}H-NMR (MeOH d_4): δ = 3.81 (3H, s, CH_3), 6.93-7.11 (3H, m, ArH), 7.37-7.61 (6H, m, ArH).

[0317] HPLC: retention time 3.11 min.

Experiment 13.17

Preparation and Analysis of Compound 12

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide

[0318] (Protocol A) - 2-(trifluoromethoxy)phenyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 457 (M+H ^{81}Br, 100), 455 (M+H ^{79}Br, 95).

^{1}H-NMR (DMSO d_6): δ = 3.79 (3H, s, CH_3), 7.06-7.18 (2H, m, ArH), 7.38-7.49 (2H, m, ArH), 7.51-7.62 (2H, m, ArH), 7.65 (1H, m, ArH), 7.71 (1H, s, ArH), 8.24 (1H, dd, J=1.1, 8.2, ArH), 8.56 (1H, s, NH), 9.49 (1H, s, NH).

[0319] HPLC: retention time 3.40 min.

Experiment 13.18

Preparation and Analysis of Compound 13

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl)carboxamide

[0320] (Protocol A) - 2-nitrophenyl isocyanate;

yellow solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 418 (M+H ^{81}Br, 98), 416 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ = 3.79 (3H, s, NCH_3), 7.14 (1H, m, ArH), 7.24 (1H, m, ArH), 7.50 (1H, t, J=7.7, ArH), 7.60 (2H, m, ArH), 7.67 (1H, s, ArH), 7.71 (1H, s, ArH), 8.10 (1H, m, ArH), 8.29 (1H, m, ArH), 9.65 (1H, s, NH), 10.09 (1H, s, NH).

[0321] HPLC: retention time 3.10 min (Method A).

Experiment 13.19

Preparation and Analysis of Compound 14

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl)carboxamide

[0322] (Protocol A) – 4-methoxyphenyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 403 (M+H ^{81}Br, 100), 401 (M+H ^{79}Br, 96).

^{1}H-NMR (DMSO d_6): δ = 3.71 (3H, s, OCH_3), 3.79 (3H, s, NCH_3), 6.87 (2H, d, J=8.9, ArH), 7.06 (1H, d, J=7.5, ArH), 7.39 (2H, d, J=8.9, ArH), 7.45-7.61 (3H, m, ArH), 7.65 (1H, s, ArH), 8.52 (1H, s, NH), 8.84 (1H, s, NH).

[0323] HPLC: retention time 3.08 min.

Experiment 13.20

Preparation and Analysis of Compound 15

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl)carboxamide

[0324] (Protocol A) – *o*-tolyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 387 (M+H ^{81}Br, 94), 385 (M+H ^{79}Br, 100).

^{1}H-NMR (MeOH d_4): δ = 2.29 (3H, s, CH_3), 3.81 (3H, s, NCH_3), 7.03 (1H, dt, J=1.1,7.5, ArH), 7.09 (1H, dt, J=1.1, 7.5, ArH), 7.13-7.22 (2H, m, ArH), 7.45 (1H, t, J=7.9, ArH), 7.49-7.57 (2H, m, ArH), 7.60-7.68 (2H, m, ArH).

[0325] HPLC: retention time 2.96 min.

Experiment 13.21

Preparation and Analysis of Compound 16

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl)phenyl)carboxamide

[0326] (Protocol A) – 4-(trifluoromethyl)phenyl isocyanate; colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 441 (M+H ^{81}Br, 94), 439 (M+H ^{79}Br, 100).

^{1}H-NMR (MeOH d_4): δ = 3.82 (3H, s, CH_3), 7.04-7.16 (3H, m, ArH), 7.20-7.47 (6H, m, ArH).

[0327] HPLC: retention time 3.56 min. :

Experiment 13.22

Preparation and Analysis of Compound 17

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl)carboxamide

[0328] (Protocol A) – 3-chlorophenyl isocyanate; colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 409 (M+H ^{81}Br ^{37}Cl, 26), 407 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 405 (M+H ^{79}Br ^{35}Cl, 70).

^{1}H-NMR (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.04 (1H, m, ArH), 7.10 (1H, m, ArH), 7.28 (2H, m, ArH), 7.47 (1H, t, J=7.8, ArH), 7.55 (1H, m, ArH), 7.63 (1H, m, ArH), 7.68 (1H, s, ArH), 7.73 (1H, m, ArH), 9.04 (2H, s, NH).

[0329] HPLC: retention time 3.20 min (Method A).

Experiment 13.23

Preparation and Analysis of Compound 18

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl)carboxamide

[0330] (Protocol A) – 2-chlorophenyl isocyanate; colorless solid (EtOAc/hexane).

MS (ES+): *m/z* (%) = 409 (M+H ^{81}Br ^{37}Cl, 24), 407 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 405 (M+H ^{79}Br ^{35}Cl, 72).

^{1}H-NMR (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.03 (1H, m, ArH), 7.11 (1H, m, ArH), 7.28 (1H, m, ArH), 7.35-7.53 (3H, m, ArH), 7.55 (1H, s, ArH), 7.62 (1H, m, ArH), 8.11 (1H, m, ArH).

[0331] HPLC: retention time 3.13 min.

Experiment 13.24

Preparation and Analysis of Compound 19

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)phenyl)carboxamide

[0332] (Protocol A) – 4-isopropylphenyl isocyanate;
colorless solid (THF/hexane).
MS (ES+): *m/z* (%) = 415 (M+H ^{81}Br, 100), 413 (M+H ^{79}Br, 92).
^{1}H-NMR (MeOH d_4): δ = 1.23 (6H, d, J=6.8, 2xCH_3), 2.86 (1H, septet, J=6.8, CH), 3.82 (3H, s, NCH_3), 7.09 (1H, m, ArH), 7.16 (2H, d, J=7.6, ArH), 7.31 (2H, d, J=7.6, ArH), 7.42-7.51 (2H, m, ArH), 7.54 (1H, s, ArH), 7.59 (1H, m, ArH).

[0333] HPLC: retention time 3.66 min.

Experiment 13.25

Preparation and Analysis of Compound 20

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl)carboxamide

[0334] (Protocol A) – 3-methoxyphenyl isocyanate;
colorless solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 403 (M+H ^{81}Br, 100), 401 (M+H ^{79}Br, 96).
^{1}H-NMR (MeOH d_4): δ = 3.73 (3H, s, OCH_3), 3.81 (3H, s, NCH_3), 6.59 (1H, m, ArH), 6.91 (1H, m, ArH), 7.08 (1H, m, ArH), 7.14 (2H, m, ArH), 7.39-7.61 (4H, m, ArH).

[0335] HPLC: retention time 2.90 min.

Experiment 13.26

Preparation and Analysis of Compound 21

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl)carboxamide

[0336] (Protocol A) – *m*-tolyl isocyanate; :
colorless solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 387 (M+H ^{81}Br, 100), 385 (M+H ^{79}Br, 96).
^{1}H-NMR (DMSO d_6): δ = 2.26 (3H, s, CH_3), 3.76 (3H, s, NCH_3), 6.79 (1H, m, ArH), 7.06-7.22 (3H, m, ArH), 7.29 (1H, m, ArH), 7.43-7.62 (3H, m, ArH), 7.68 (1H, s, ArH), 8.65 (1H, s, NH), 8.89 (1H, s, NH).

[0337] HPLC: retention time 3.05 min (Method A).

Experiment 13.27

Preparation and Analysis of Compound 22

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)-carboxamide

[0338] (Protocol B) – *N*-methyl-4-(trifluoromethoxy)aniline;
pale yellow solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 471 (M+H ^{81}Br, 88), 469 (M+H ^{79}Br, 100).
^{1}H-NMR (MeOH d_4): δ = 3.35 (3H, s, NCH_3), 3.81 (3H, s, NCH_3), 7.09 (1H, m, ArH), 7.25-7.51 (8H, m, ArH).

[0339] HPLC: retention time 3.56 min (Method A).

Experiment 13.28

Preparation and Analysis of Compound 23

N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide
(Protocol B) – 4-*tert*-butylaniline;

[0340] colorless solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 429 (M+H ^{81}Br, 98), 427 (M+H ^{79}Br, 100).
^{1}H-NMR (DMSO d_6): δ = 1.27 (9H, s, 3xCH_3), 3.79 (3H, s, NCH_3), 7.07 (1H, d, J=7.5, ArH), 7.29 (2H, d, J=8.7, ArH), 7.37 (2H, d, J=8.7, ArH), 7.45 (1H, t, J=7.5, ArH), 7.51-7.60 (2H, m, ArH), 7.66 (1H, s, ArH), 8.65 (1H, s, NH), 8.83 (1H, s, NH).

[0341] HPLC: retention time 3.77 min.

Experiment 13.29

Preparation and Analysis of Compound 24

N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide
(Protocol B) – *N*,*N*-dimethyl-*p*-phenylenediamine;

[0342] colorless solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 416 (M+H ^{81}Br, 96), 414 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ = 2.86 (6H, s, NCH_3), 3.80 (3H, s, NCH_3), 6.80 (2H, m, ArH), 7.09 (1H, d, J=7.7, ArH), 7.28 (2H, m, ArH), 7.42 (1H, t, J=7.8, ArH), 7.52 (1H, m, ArH), 7.59 (1H, s, ArH), 7.67 (1H, s, ArH), 8.45 (1H, s, NH), 8.75 (1H, s, NH).

[0343] HPLC: retention time 2.07 min (Method A).

Experiment 13.30

Preparation and Analysis of Compound 25

N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino) carboxamide (Protocol B) – 3,5-dichloro-4-methylphenylamine;

[0344] colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 457 (M+H, 35), 455 (M+H, 100), 453 (M+H, 65).

^{1}H-NMR (DMSO d_6): δ = 2.32 (3H, s, CH_3), 3.79 (3H, s, NCH_3), 7.11 (1H, d, J=7.4, ArH), 7.46 (1H, t, J=7.8, ArH), 7.50-7.64 (4H, m, ArH), 7.68 (1H, s, ArH), 9.02 (1H, s, NH), 9.09 (1H, s, NH).

[0345] HPLC: retention time 3.66 min.

Experiment 13.31

Preparation and Analysis of Compound 26

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethylthio)phenyl) carboxamide (Protocol B) – 4-(trifluoromethylthio)aniline;

[0346] colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 473 (M+H ^{81}Br, 100), 471 (M+H ^{79}Br, 94).

^{1}H-NMR (DMSO d_6): δ = 3.81 (3H, s, NCH_3), 7.11 (1H, d, J=7.5, ArH), 7.47 (1H, t, J=7.9, ArH), 7.51-7.63 (6H, m, ArH), 7.66 (1H, s, ArH), 9.03 (1H, s, NH), 9.16 (1H, s, NH).

HPLC: retention time 3.76 min.

Experiment 13.32

Preparation and Analysis of Compound 31

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl)carboxamide

[0347] (Protocol B) – cyclohexylamine; :

colorless solid, m.p. 155.5-156.3°C (EtOAc/hexane).

MS (ES+): m/z (%) = 379 (M+H ^{81}Br, 93), 377 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ = 1.07-1.34 (5H, m, 5xCH), 1.52 (1H, m, CH), 1.63 (2H, m, 2xCH), 1.76 (2H, m, 2xCH), 3.48 (1H, m, NCH), 3.74 (3H, s, CH_3), 6.15 (1H, d, J=7.8, ArH), 6.98 (1H, d, J=7.5, ArH), 7.32-7.43 (2H, m, ArH), 7.51 (1H, m, NH), 7.62 (1H, s, ArH), 8.50 (1H, s, NH).

[0348] HPLC: retention time 3.16 min (Method A). :
TLC: retention factor 0.35 (50% EtOAc/hexane).

Experiment 13.33

Preparation and Analysis of Compound 32

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl)carboxamide

[0349] (Protocol B) – benzylamine;
colorless solid, m.p. 144.5-146.2°C (EtOAc/hexane).
IR: $_{max}$ = 1622, 1565, 1467, 1374, 1239, 973, 802, 752, 695 cm^{-1}.
MS (ES+): *m/z* (%) = 387 (M+H ^{81}Br, 89), 385 (M+H ^{79}Br, 100).
^{1}H-NMR (CD_3OD): δ = 3.81 (3H, s, CH_3), 4.40 (2H, s, CH_2), 7.05 (1H, m, ArH), 7.19-7.51 (9H, m, ArH).

[0350] HPLC: retention time 3.06 min (Method A).

Experiment 13.34

Preparation and Analysis of Compound 27

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl)carboxamide

[0351] (Protocol A) – 2-fluorophenyl isocyanate;
colorless solid (DCM/hexane).
MS (ES+): *m/z* (%) = 391 (M+H ^{81}Br, 100), 389 (M+H ^{79}Br, 90).
^{1}H-NMR (MeOH d_4): δ = 3.79 (3H, s, NCH_3), 7.00-7.11 (4H, m, ArH), 7.40-7.56 (3H, m, ArH), 7.61 (1H, m, ArH), 8.09 (1H, m, ArH).

[0352] HPLC: retention time 3.01 min.

Experiment 13.35

Preparation and Analysis of Compound 28

2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino)benzamide

[0353] (Protocol B) – 2-aminobenzamide;
colorless solid (EtOAc/hexane).
MS (ES+): m/z (%) = 399 (M+H -17 ^{81}Br, 100), 397 (M+H - 17 ^{79}Br, 94).
^{1}H-NMR (DMSO d_6): δ = 3.79 (3H, s, NCH_3), 6.93-7.10 (2H, m, ArH), 7.45 (2H, t, J=7.8, ArH), 7.59-7.72 (5H, m, ArH), 8.22 (2H, m), 9.92 (1H, s, NH), 10.69 (1H, s, NH).

[0354] HPLC: retention time 2.88 min.

Experiment 13.36

Preparation and Analysis of Compound 29

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl)carboxamide

[0355] (Protocol B) – 4-aminobenzonitrile;
colorless solid (EtOAc/hexane).
MS (ES+): m/z (%) = 398 (M+H ^{81}Br, 100), 396 (M+H ^{79}Br, 96).
^{1}H-NMR (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.12 (1H, m, ArH), 7.46-7.57 (3H, m, ArH), 7.62-7.69 (5H, m, ArH).

[0356] HPLC: retention time 3.12 min.

Experiment 13.37

Preparation and Analysis of Compound 30

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl)carboxamide

[0357] (Protocol B) – 2-aminobenzonitrile;
colorless solid (EtOAc/hexane).
MS (ES+): m/z (%) = 398 (M+H ^{81}Br, 95), 396 (M+H ^{79}Br, 100).
^{1}H-NMR ($CDCl_3$): δ = 3.79 (3H, s, CH_3), 7.13-7.28 (2H, m, ArH), 7.49 (1H, t, J=7.8, ArH), 7.57 (1H, m, ArH), 7.62 (1H, m, ArH), 7.65-7.71 (2H, m, ArH), 7.78 (1H, m, ArH), 8.07 (1H, d, J=8.6, ArH), 8.83 (1H, s, NH), 9.62 (1H, s, NH).

[0358] HPLC: retention time 3.05 min (Method A).

Experiment 13.38

Preparation and Analysis of Compound 33

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenylmethyl)carboxamide

[0359] (Protocol B) – 4-fluorobenzylamine;
colorless solid, m.p. 185.5-186.6°C (EtOAc/hexane).
MS (ES+): m/z (%) = 405 (M+H ^{81}Br, 97), 403 (M+H ^{79}Br, 100).
^{1}H-NMR (DMSO d_6): δ = 3.75 (3H, s, CH_3), 4.28 (2H, d, J=6.0, CH_2), 6.73 (1H, t, J=5.9, NH), 7.01 (1H, d, J=7.5, ArH), 7.10-7.18 (2H, m, ArH), 7.27-7.41 (4H, m, ArH), 7.56 (1H, s, ArH), 7.62 (1H, s, ArH), 8.82 (1H, s, NH).

[0360] HPLC: retention time 3.10 min (Method A).

[0361] TLC: retention factor 0.25 (50% EtOAc/hexane).

Experiment 13.39

Preparation and Analysis of Compound 34

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-dimethoxyphenylmethyl)carboxamide

[0362] (Protocol B) – 3,4-dimethoxybenzylamine:
colorless solid, m.p. 174.9-175.5°C (EtOAc/hexane).
MS (CI+): m/z (%) = 447 (M+H ^{81}Br, 100), 445 (M+H ^{79}Br, 92).
^{1}H-NMR (DMSO d_6): δ = 3.71 (3H, s, CH_3), 3.73 (3H, s, CH_3), 3.76 (3H, s, CH_3), 4.22 (2H, d, J=5.8, CH_2), 6.62 (1H, t, J=5.7, NH), 6.80 (1H, m, ArH), 6.89 (2H, m, ArH), 6.98 (1H, m, ArH), 7.36-7.51 (3H, m, ArH), 7.63 (1H, s, ArH), 8.76 (1H, s, NH).

[0363] HPLC: retention time 2.86 min (Method A).

[0364] TLC: retention factor 0.20 (50% EtOAc/hexane).

Experiment 13.40

Preparation and Analysis of Compound 35

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-trimethoxyphenylmethyl)carboxamide

[0365] (Protocol B) – 3,4,5-trimethoxybenzylamine;
colorless solid (EtOAc/hexane).
MS (CI+): m/z (%) = 477 (M+H ^{81}Br, 100), 475 (M+H ^{79}Br, 95).

^{1}H-NMR (DMSO d_6): δ = 3.63 (3H, s, OCH_3), 3.75 (9H, s, $3xCH_3$), 4.21 (1H, d, J=5.9, CH_2), 6.61 (2H, s, ArH), 6.65 (1H, t, J=5.9, NH), 6.99 (1H, m, ArH), 7.40 (1H, t, J=7.7, ArH), 7.45 (1H, m, ArH), 7.56 (1H, m, ArH), 7.64 (1H, s, ArH), 8.77 (1H, s, NH).

[0366] HPLC: retention time 5.91 min (Method B).

[0367] TLC: retention factor 0.50 (50% EtOAc/hexane).

Experiment 13.41

Preparation and Analysis of Compound 36

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl)amino)carboxamide

[0368] (Protocol B) – 2-methylbenzylamine;

colorless solid (EtOAc/hexane).

MS (CI+): m/z (%) = 401 (M+H ^{81}Br, 96), 399 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ = 2.28 (3H, s, CH_3), 3.76 (3H, s, NCH_3), 4.28 (1H, d, J=5.8, CH_2), 6.60 (1H, t, J=5.8, NH), 7.01 (1H, m, ArH), 7.15 (3H, m, ArH), 7.24 (1H, m, ArH), 7.38-7.50 (2H, m, ArH), 7.57 (1H, m, ArH), 7.65 (1H, s, ArH), 8.77 (1H, s, NH).

[0369] HPLC: retention time 2.74 min (Method A).

[0370] TLC: retention factor 0.20 (50% EtOAc/hexane).

Experiment 13.42

Preparation and Analysis of Compound 37

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenylmethyl)carboxamide

[0371] (Protocol B) – 4-methoxybenzylamine;

colorless solid (EtOAc/hexane).

MS (CI+): m/z (%) = 417 (M+H ^{81}Br, 94), 415 (M+H ^{79}Br, 100).

^{1}H-NMR (DMSO d_6): δ = 3.72 (3H, s, CH_3), 3.77 (3H, s, NCH_3), 4.22 (1H, d, J=5.9, CH_2), 6.62 (1H, t, J=5.9, NH), 6.90 (2H, d, J=8.8, ArH), 7.00 (1H, m, ArH), 7.23 (2H, d, J=8.8, ArH), 7.39 (1H, t, J=7.8, ArH), 7.43 (1H, m, ArH), 7.56 (1H, m, ArH), 7.64 (1H, s, ArH), 8.73 (1H, s, NH).

[0372] HPLC: retention time 6.41 min (Method B).

[0373] TLC: retention factor 0.25 (50% EtOAc/hexane).

Experiment 13.43

Preparation and Analysis of Compound 38

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide

[0374] (Protocol B) – 2-(4-methoxyphenyl)ethylamine;
colorless solid (EtOAc/hexane).
MS (ES+): *m/z* (%) = 431 (M+H ^{81}Br, 95), 429 (M+H ^{79}Br, 100).
^{1}H-NMR (DMSO d_6): δ = 2.68 (2H, t, J=7.1, CH_2), 3.31 (2H, m, CH_2), 3.71 (3H, s, CH_3), 3.77 (3H, s, CH_3), 6.16 (1H, t, J=5.8, NH), 6.87 (2H, d, J=8.6, ArH), 6.99 (1H, dt, J=1.4, 7.3, ArH), 7.16 (2H, d, J=8.6, ArH), 7.33-7.48 (2H, m, ArH), 7.52 (1H, m, ArH), 7.63 (1H, s, ArH), 8.71 (1H, s, NH).

[0375] HPLC: retention time 6.62 min (Method B).

EXAMPLE 14

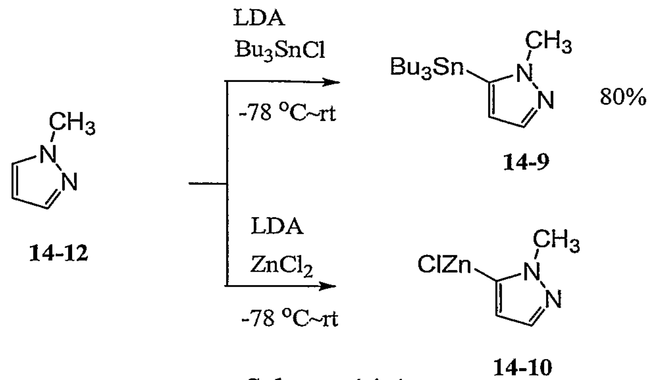
Experiments 14.1 – 14.19

General Synthetic Strategies, Preparation and Analysis of Compounds

[0376] Compounds of certain embodiments of the invention were prepared according to the procedures below.

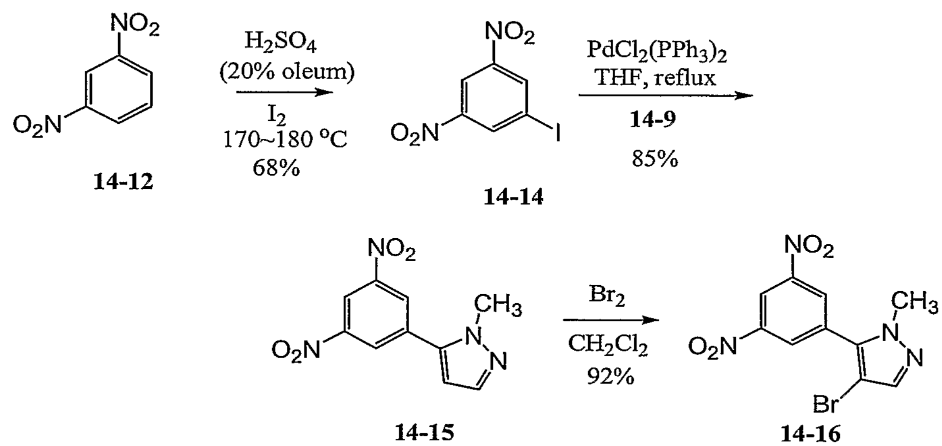
General Synthetic Strategies

[0377] Tributyltin pyrazole **14-9** was synthesized from pyrazole **14-12** in 80 % chemical yield. Pyrazole **14-12** was directly lithiated with LDA at –78 °C followed by quenching with Bu_3SnCl. Tributyltin pyrazole **14-9** is fairly stable on silica gel and can be stored at room temperature without any decomposition for up to one month in the air. Zinc pyraole **14-10** was also formed under lithiation with LDA or *n*-BuLi at –78 °C followed by quenching with $ZnCl_2$ in high yields. Zinc pyraole **14-10** was freshly synthesized for coupling reactions (Scheme **14-1**).



Scheme **14-1**

[0378] 1,3-Dinitrobenzene **14-13** was commercially available and iodinated with I_2 and H_2SO_4 (oleum) to afford iodobenzene **14-14** in 68 % yield. Iodobenzene **14-14** was coupled with tributyltin pyrazole **14-9** under 7 % $PdCl_2(PPh_3)_2$ to afford coupled product **14-15** in 85 % yield which could also be separable by recrystallization in ethanol and synthesize in quantity (i.e., 20g scale). Regiospecific bromination of **14-16** occurred smoothly under Br_2 in dichloromethane at room temperature (Scheme **14-2**).

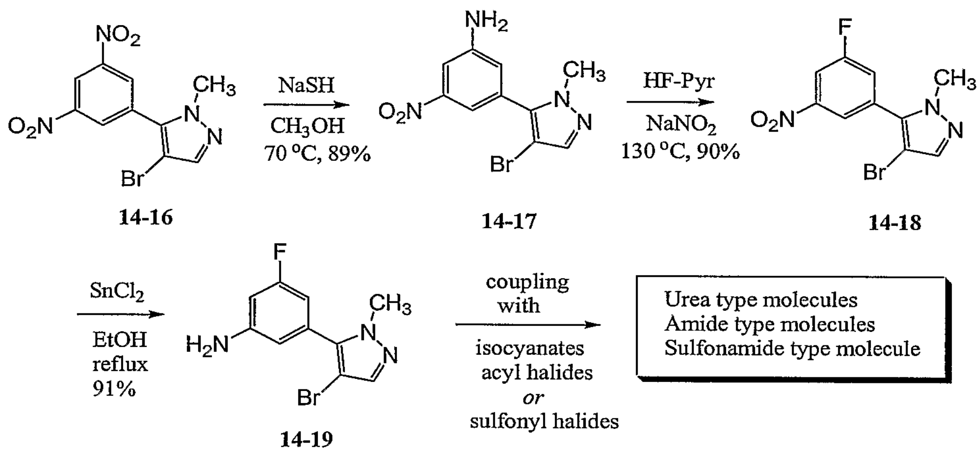


Scheme **14-2**

[0379] A number of reagents have been used for selective reduction of nitroaromatic compounds, the most common being alcoholic basic hydrogen sulfide, alcoholic ammonium sulphide, and alcoholic sodium polysulphide. However, the product amines from these reactions are generally obtained in low yields and are often difficult to purify. The hydrosulfide-induced reaction was investigated intensively by Idoux and is superior to the previously reported method. Based on this

result, dinitro **14-16** was reduced to aniline **14-17** with NaSH in CH_3OH; 2.7 equivalents of NaSH were needed to complete the reaction. Double reduced compound was also detected on the LCMS, but it was less than 5 % (Scheme **14-3**).

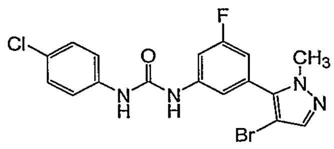
[0380] Aniline **14-17** was also fluorinated under HF•Pyr and $NaNO_2$ to furnish **14-18** in 90 % yield. **14-18** could be reduced with $SnCl_2$ as a usual way to form flouroaniline **14-19** in 91 % yield. The precursor **14-19** was coupled with various isocyanates, acyl halides and sulfonyl halides to form urea, amide and sulfonamide type molecules respectively in good yields (Scheme **14-3**).



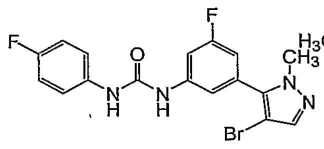
Scheme **14-3**

[0381] The following contains the list of representative fluorinated compounds synthesized (**TABLE 14-1**).

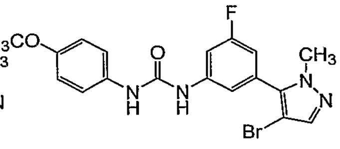
Table **14-1** Compounds of the invention containing a fluoride functionality.



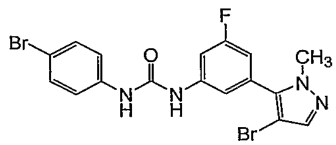
Compound **96**



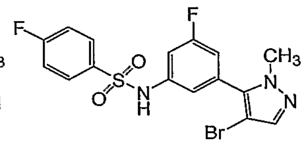
Compound **100**



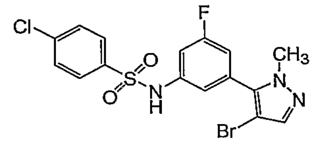
Compound **101**



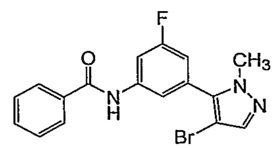
Compound **98**



Compound **97**

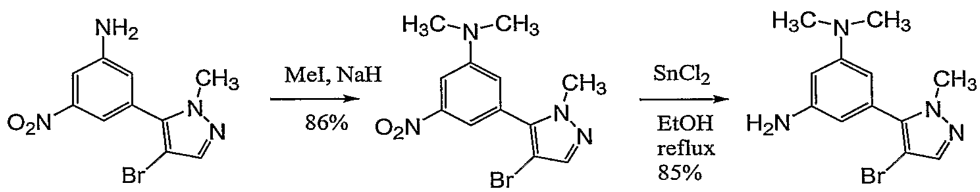


Compound **103**



Compound **183**

[0382] In addition, as shown in Scheme **14-3,** aniline **14-17** was also alkylated with 2 equivalents of CH_3I and NaH at room temperature in 86 % yield. Finally, **14-17** was reduced with $SnCl_2 \cdot H_2O$ in EtOH at a reflux condition to furnish the aminomethylated precursor **14-21** in 85 % yield (Scheme **14-4**).

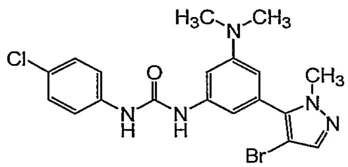


14-17 **14-20** **14-21**

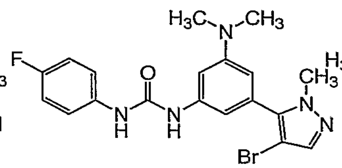
Scheme **14-4**

[0383] Aniline **14-21** was coupled with various isocyanates, acyl chlorides and sulfonyl chlorides to form aminodimethylated compound of the invention in high yields (**TABLE 14-2**).

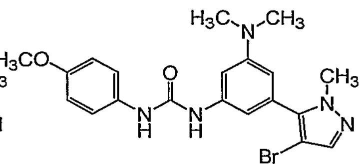
Table **14-2** Compounds of the invention containing *N, N*-dimethylamino fuctionality.



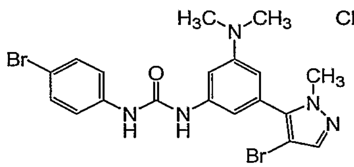
Compound **113**



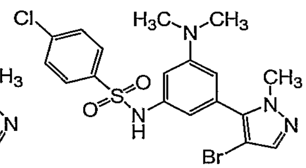
Compound **129**



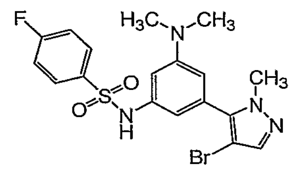
Compound **136**



Compound **105**

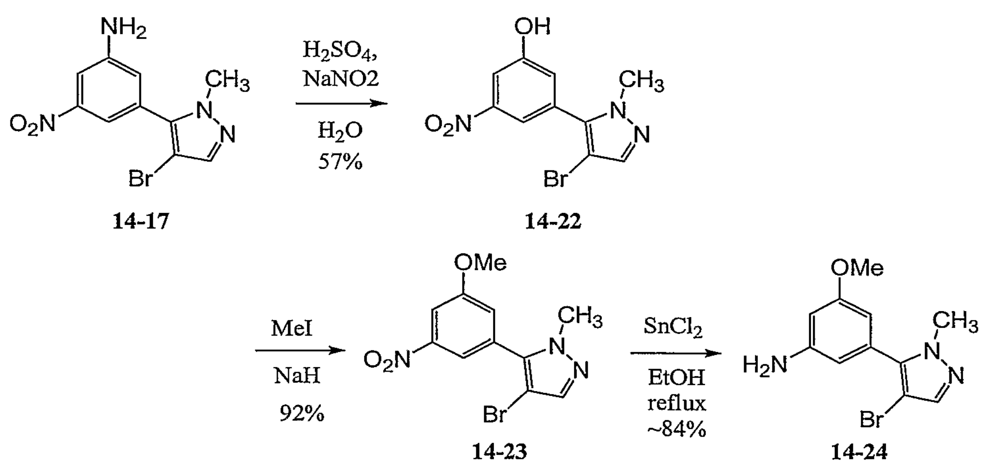


Compound **119**



Compound **144**

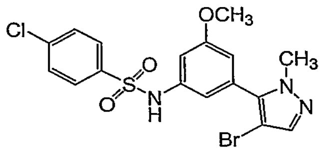
[0384] The amino group on aniline **14-17** was transformed into a hydroxy group under H_2SO_4 and $NaNO_2$ to give phenol **14-22** in a 57 % yield. Phenol **14-22** was methylated with MeI and NaH in DMF followed by reduction with $SnCl_2{\bullet}H_2O$ in EtOH providing aniline **14-24** in good yields (Scheme **14-5**).



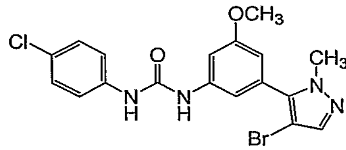
Scheme **14-5**

[0385] Aniline **14-24** was coupled with various isocyanates, acyl chlorides and sulfonyl chlorides to furnish the compounds of the invention containing a methoxy group (**TABLE 14-3**).

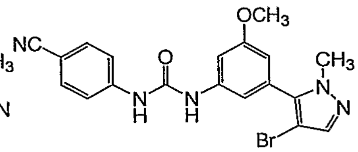
Table **14-3** Compounds of the invention containing methoxy fuctionality.



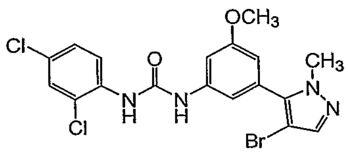
Compound **152**



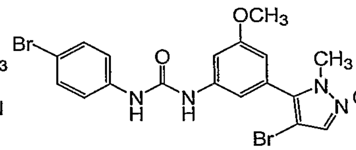
Compound **158**



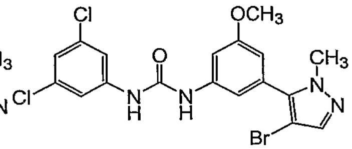
Compound **163**



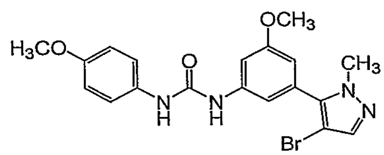
Compound **159**



Compound **154**

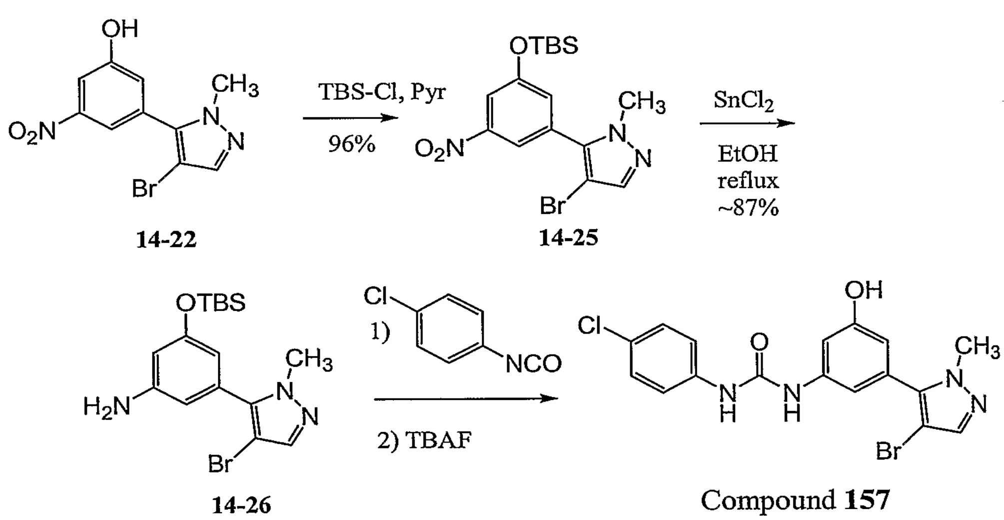


Compound **156**



Compound **162**

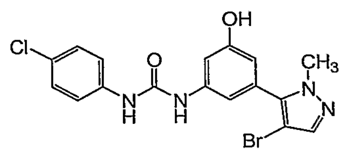
[0386] An introduction of a hydroxy group on the aromatic ring was also attempted. Phenol **14-22** was protected with TBS-Cl in pyridine at room temperature followed by reduction with $SnCl_2 \cdot H_2O$ in EtOH to afford silylether **14-25** in high yield. After reduction with $SnCl_2$, aniline **14-26** was coupled with 4-chlorophenyl isocyanate at room temperature and deprotected with TBAF *in situ* to furnish Compound **157** of the invention in 89 % yield after column chlomatography on silica gel (Scheme **14-6**).



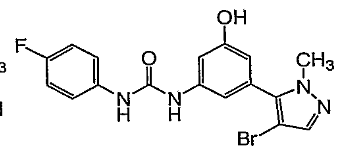
Scheme **14-6**

[0387] The list of compounds of the invention containing a hydroxy functionality is shown below (**TABLE 14-4**).

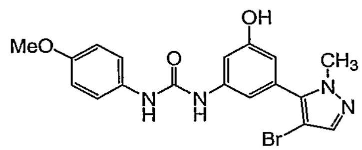
Table **14-4** Compounds of the invention containing hydroxy functionality



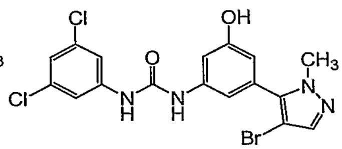
Compound **157**



Compound **151**

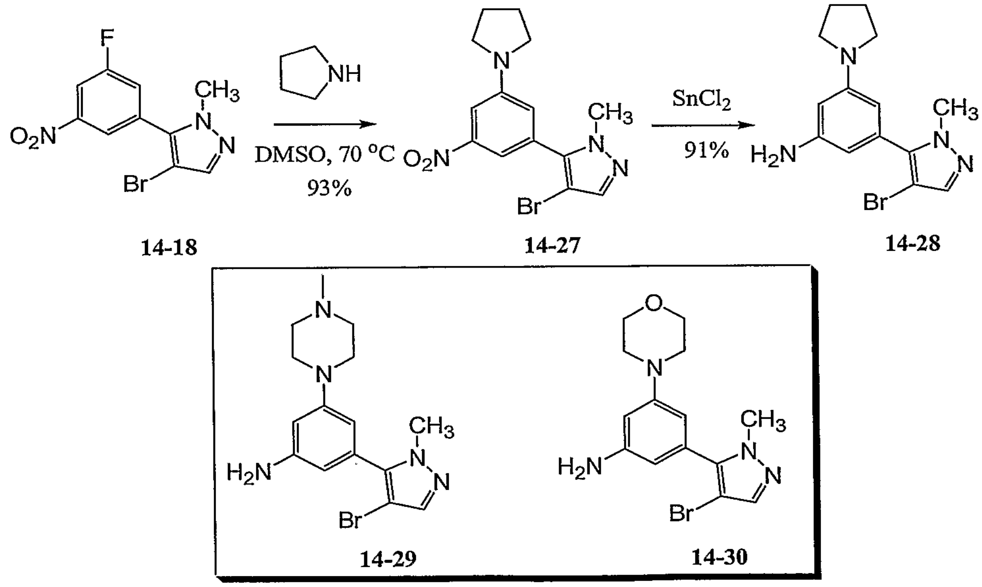


Compound **161**



Compound **150**

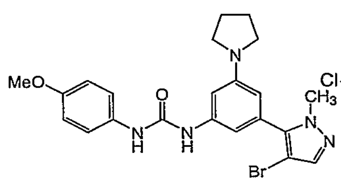
[0388] Several attempts for introduction of cycloamines on the aromatic group have been made. The direct substitution reaction of various cyclic amines under mild conditions gave desired products. For these reactions, DMSO is the choice of solvents (Scheme **14-7**).



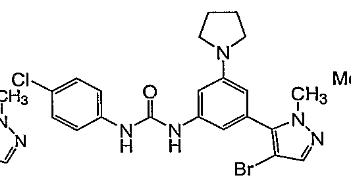
Scheme **14-7**

[0389] Fluoro phenyl **14-18** was treated with pyrrolidine in DMSO to afford **14-27** in 93% yield. Subsequently, pyrrolidine **14-27** was reduced with four equivalents of $SnCl_2 \cdot 2H_2O$ in EtOH to furnish the precursor **14-28** in 91 % yield. *N*-Methyl piperazine and morpholine were introduced to the aromatic group in the same manner to achive the precursors **14-29** and **14-30** respectively. With these precursors available, the coupling reactions were compelted with various isocyanates, acyl chlorides and sulfonyl chlorides. **TABLES 14-5, 14-6** and **14-7** show additional compounds of the invention.

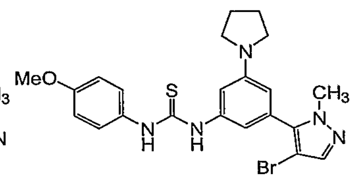
Table **14-5** Compounds of the invention containing pyrrolidine fuctionality.



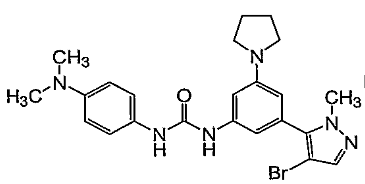
Compound **125**



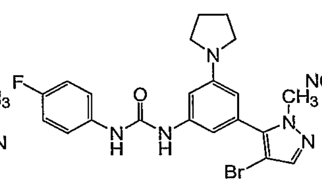
Compound **141**



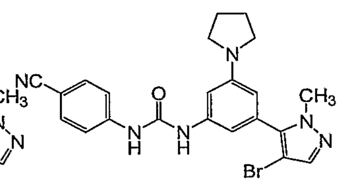
Compound **115**



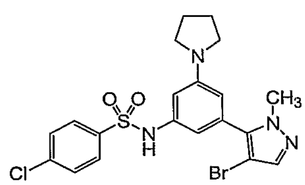
Compound **110**



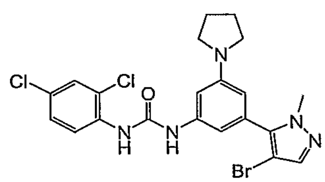
Compound **131**



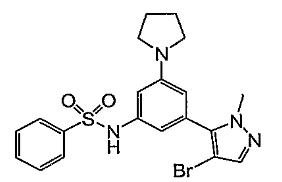
Compound **143**



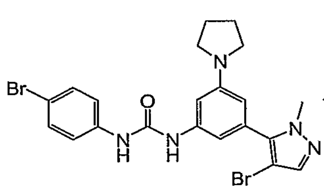
Compound **184**



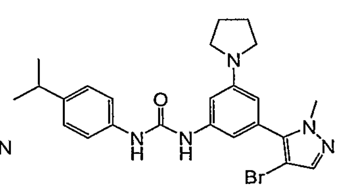
Compound **122**



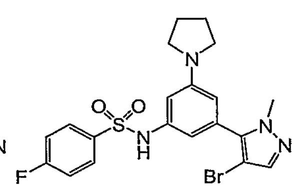
Compound **145**



Compound **109**

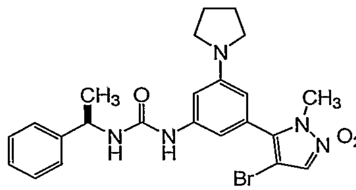


Compound **148**

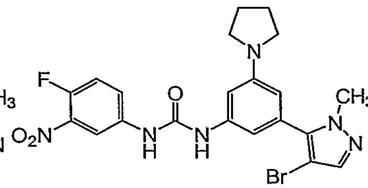


Compound **118**

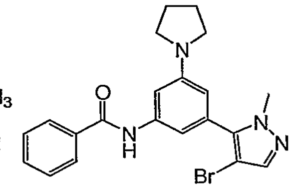
Table **14-5** Continued



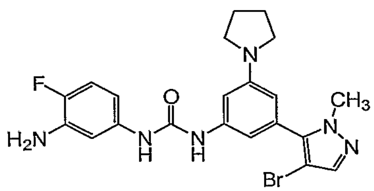
Compound **106**



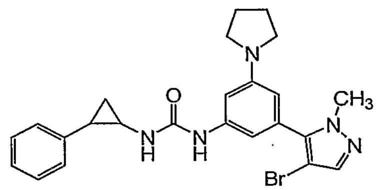
Compound **137**



Compound **108**

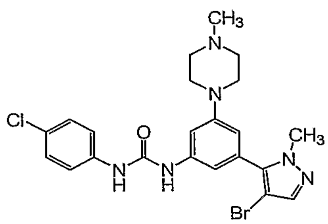


Compound **135**

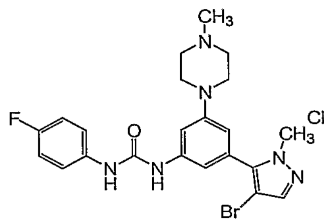


Compound **140**

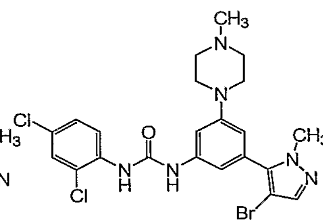
Table **14-6** Compounds of the invention containing *N*-methyl piperazine fuctionality.



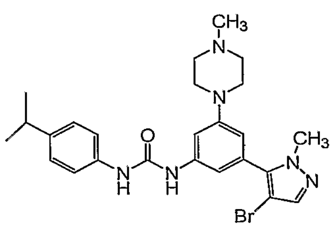
Compound **117**



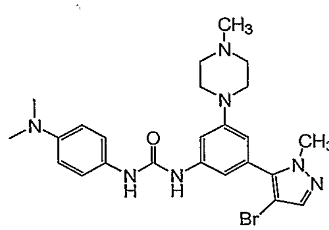
Compound **124**



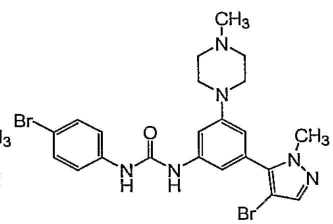
Compound **133**



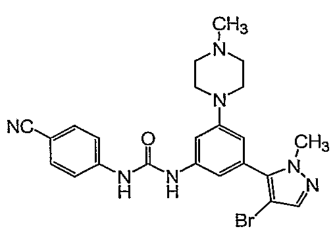
Compound **116**



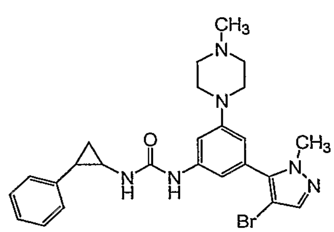
Compound **147**



Compound **112**

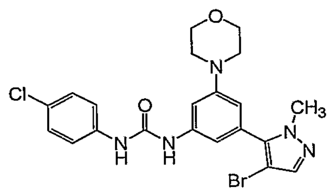


Compound **127**

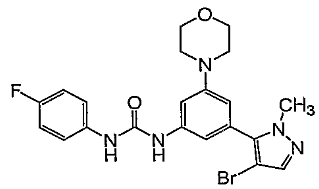


Compound **132**

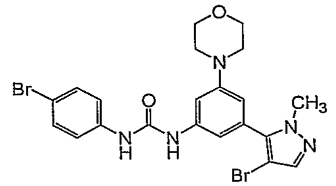
Table **14-7** Compounds of the invention containing morpholine fuctionality.



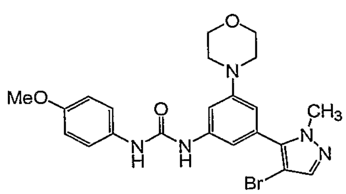
Compound **121**



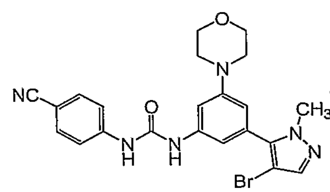
Compound **120**



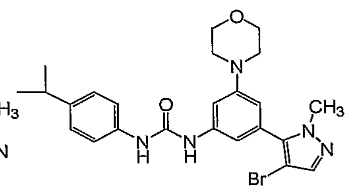
Compound **142**



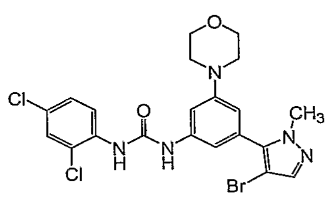
Compound **146**



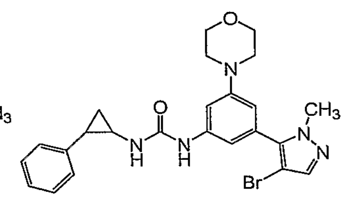
Compound **128**



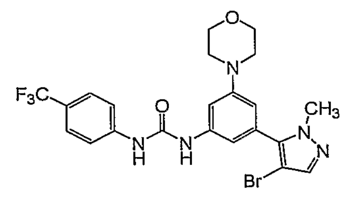
Compound **111**



Compound **107**



Compound **126**

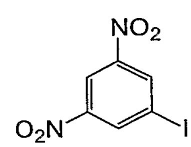


Compound **134**

Experiment 14.1

Preparation and Analysis of Compound

1,3-Dinitro iodobenzene **14-14:**

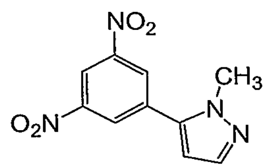


[0390] 1,3-Dinitobenzene (10 g, 59.5 mmol) and I_2 (7.5 g, 29.5 mmol) were dissolved in 20% oleum (75.9 g) and heated to 170 °C for 45 min. The reaction mixture was maintained at 170~180 °C for 1hr. The temperature was lowered to room temperature. The mixture was poured into crushed ice (500 g) and stirred for 2 hrs. The solid material was filtered and washed with H_2O (500 mL). The solid was dissolved in EtOAc (250 mL) and washed with H_2O (150 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum to afford to the desired product **14-14** in 62 % yield (10.8 g). $R_f = 0.52$ (EtOAc/Hex = 1/4).

Experiment 14.2

Preparation and Analysis of Compound

Pyrazole **14-15**

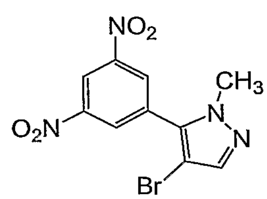


[0391] Iodobenzen **14-14** (2 g, 6.8 mmol) was dissolved in anhydrous THF (20 mL) and treated with tributyltin pyrazole **14-9** (2.5 g, 6.8 mmol, see Scheme **14-1**) and $PdCl_2(PPh_3)_2$ (0.48 g, 0.68 mmol). The mixture was heated to reflux. After refluxing for 12hrs, the reaction mixture was cooled to room temperature and concentrated under vaccum. The residue was dissolved in EtOAc (50 mL) and washed with H_2O (50 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The crude compound was recrystallized in EtOH (30 mL) to afford the desired coupled product **14-15** (1.41 g, 84 %). $R_f = 0.5$ (EtOAc/Hex = 1/3).

Experiment 14.3

Preparation and Analysis of Compound

Bromo pyrazole **14-16**

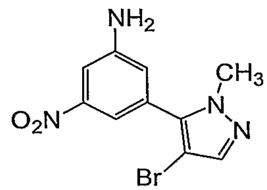


[0392] To a solution of **14-15** (0.4 g, 1.6 mmol) in dichloromethane (5 mL), was added dropwise Br_2 (91 μL, 1.77 mmol) in dichloromethane (1 mL) for 5 min at 0 °C. After addition of Br_2, the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H_2O (10 mL) and triturated with EtOH to afford yellowish crystals of the desired product (0.46 g, 92 %) $R_f = 0.72$ (EtOAc/Hex = 1/2).

Experiment 14.4

Preparation and Analysis of Compound

Aniline **14-17**

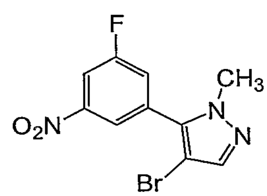


[0393] Dinitrophenyl **14-16** (0.6 g, 1.8 mmol) was dissolved in MeOH (40 mL) and toluene (10 mL) and heated to refluxing. NaSH (262 mg, 4.68 mmol) in MeOH (10 mL) was added into the solution for 45 min. The reaction mixture was stirred for 30 min at the same temperature and cooled to room temperature. The reaction mixture was concentrated under vaccum and dissolved in EtOAc (20 mL). The EtOAc was washed with H_2O (20 mL x 2) and dried over $MgSO_4$. The crude product was purified over column chromatography (R_f = 0.51, EtOAc/Hex = 1/1) to afford to a yellow solid as the desired product **14-17** (487 mg, 91 %).

Experiment 14.5

Preparation and Analysis of Compound

Fluorophenyl pyrazole **14-18**

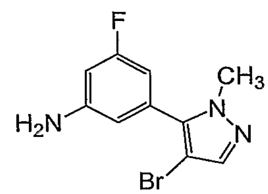


[0394] Aniline **14-17** (0.3 g, 1.01 mmol) was added into HF•Pyr (2.6 mL) at 0 °C and warmed to room temperature. After stirring for 30 min, the solution was cooled to –30 °C and $NaNO_2$ (77 mg, 1.11 mmol) added portionwise for 10 min. The reaction mixture was maintained at –30 °C for 30 min. The mixture was then heated to 145 °C and stirred for 10 min. The reaction mixture was cooled to room temperature and quenched with crushed ice (10 mL). The crude product was extracted with EtOAc (20 mL), dried over $MgSO_4$ and concentrated under vaccum. The crude material was purified by column chromatograph (EtOAc/Hex = 1/1, R_f = 0.85) to afford a yellow crystal as desired product **14-17** (275 mg, 91%).

Experiment 14.6

Preparation and Analysis of Compound

Fluoro aniline **14-19**

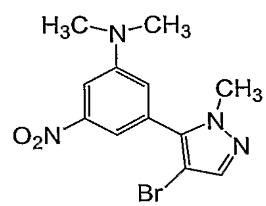


[0395] A 5 mL round-bottom flask was charged with 100 mg of **14-18** (0.33 mmol) and $SnCl_2 \cdot 2H_2O$ (0.3 g, 1.33 mmol) and dissolved in EtOH (3 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was under concentrated under vaccum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of the desired product **14-19** (79 mg, 89%).

Experiment 14.7

Preparation and Analysis of Compound

Dimethyl aniline **14-20**

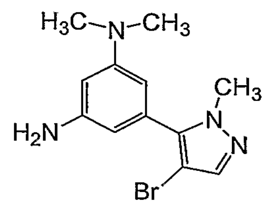


[0396] Aniline **14-17** (1.0 g, 3.36 mmol) was dissolved in DMF (5 mL) in a 10 mL round-bottom flask. The solution was cooled to 0 °C and treated with 60 % NaH (404 mg, 10.08 mmol). The reaction mixture was maintained at the same temperature for 30 min and warmed to room temperature. The mixture was quenched with 100 μL of EtOH and extracted with EtOAc (20 mL). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The residue was purified over silica gel (EA/Hex = 1/1, Rf = 0.81) to afford yellow solids as the desired product **14-20** (858 mg, 86%).

Experiment 14.8

Preparation and Analysis of Compound

Aniline **14-21**

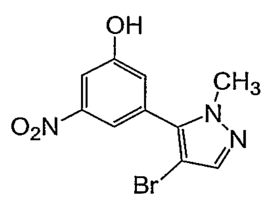


[0397] A 5 mL round-bottom flask was charged with 103 mg of **14-20** (0.33 mmol) and $SnCl_2 \cdot 2H_2O$ (0.3 g, 1.33 mmol) and dissolved in EtOH (3 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was under concentrated under vaccum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal as desired product **14-21** (82 mg, 85%).

Experiment 14.9

Preparation and Analysis of Compound

Phenol **14-22**

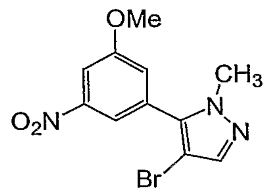


[0398] Aniline **14-17** (2 g, 6.73 mmol) was dissolved in H_2SO_4 (5 mL) and H_2O (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. The solution was treated with $NaNO_2$ (557 mg, 808 mmol) at –30 °C and stirred for 1 hr. The reaction mixture was heated to 100 °C and stirred for 1 hr. The resulting mixture was cooled to room temperature and quenched with crushed ice (10 g). The mixture was extracted with EtOAc (20 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The residue was purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.52) to afford the white crystals of desired product **14-22** (1.13 g, 57%).

Experiment 14.10

Preparation and Analysis of Compound

Anisole **14-23**

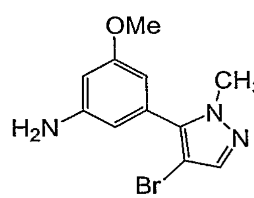


[0399] To a cooled solution of phenol **14-22** (657 mg, 2.2 mmol) in DMF (5 mL) was treated with 60 % NaH (106 mg, 2.65 mmol). The resulting mixture was stirred at 0 °C and treated with CH_3I (165 μL, 2.65 mmol). The reaction mixture was stirred for 1 hr and warmed to room temperature. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The residue was purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.75) to afford desired anisole **14-23** (629 mg, 92%).

Experiment 14.11

Preparation and Analysis of Compound

Aniline **14-24**

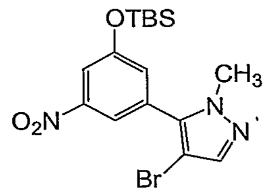


[0400] A 25 mL round-bottom flask wad charged with 103 mg of anisole **14-23** (2.08 mmol) and $SnCl_2$•$2H_2O$ (2.13 g, 8.36 mmol) and dissolved in EtOH (10 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (30 mL x 2) and H_2O (30 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desired product **14-24** (489 mg, 84 %).

Experiment 14.12

Preparation and Analysis of Compound

Silyl ether **14-25**

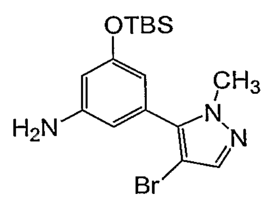


[0401] To a solution of phenol **14-22** (1g, 3.38 mmol) dissolved in pyridine (3 mL) was added TBS-Cl (611 mg, 4.05 mmol) and the resulting solution was allowed to stir for 10 hrs. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL) dried over $MgSO_4$ and concentrated under vaccum to afford crude product **14-25** (1.36 g, 96%). The crude product was used for the next step without further purification (EtOAc/Hex = 1/1, Rf = 0.89).

Experiment 14.13

Preparation and Analysis of Compound

Aniline **14-26**

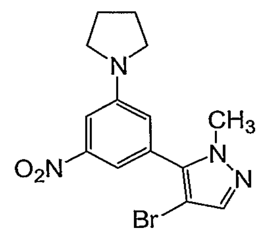


[0402] A 25 mL round-bottom flask was charged with 1.0 g of **14-25** (2.4 mmol) and $SnCl_2 \cdot 2H_2O$ (2.19 g, 9.7 mmol) and dissolved in EtOH (10 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (30 mL x 2) and H_2O (30 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desired product **14-26** (798 mg, 87 %).

Experiment 14.14

Preparation and Analysis of Compound

Pyrrolidine **14-27**

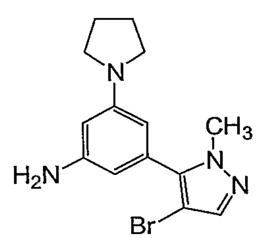


[0403] Fluorophenyl pyrazole **14-18** (2.6 g, 8.67 mmol) was directly weighed into a 50 mL round-bottom flask and dissolved in DMSO (10 mL). The solution was treated with pyrrolidine (2.2 mL, 26 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H_2O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL), dried over $MgSO_4$ and concentrated under vaccum. The residue was purified over silica gel to afford the desired product **14-27** (2.77 g, 93%).

Experiment 14.15

Preparation and Analysis of Compound

Aniline **14-28**

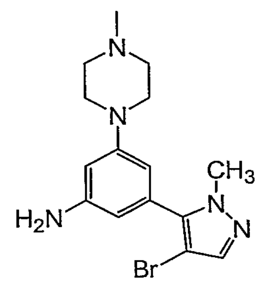


[0404] A 50 mL round-bottom flask was charged with 2.0 of Pyrrolidine **14-27** (5.7 mmol) and $SnCl_2•2H_2O$ (5.8 g, 22.8 mmol) charged dissolved in EtOH (30 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (50 mL x 2) and H_2O (50 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desire product **14-28** (1.66 g, 91 %).:

Experiment 14.16

Preparation and Analysis of Compound

N-Methylpiperazine **14-29**

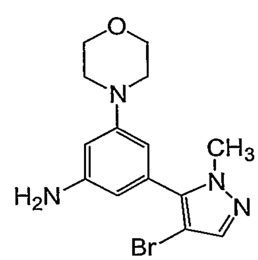


[0405] Fluorophenyl pyrazole **14-18** (2.6 g, 8.67 mmol) was directly weighed into a 50 mL round-bottom flask and dissolved in DMSO (10 mL). The solution was treated with 4-methylpiperazine (1.5 mL, 17.3 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H_2O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL), dried over $MgSO_4$ and concentrated under vaccum. The crude product was used for the next step without further purification. A 100 mL round-bottom flask was charged with the crude compound and $SnCl_2$•$2H_2O$ (8.86 g, 34.7 mmol) and dissolved in EtOH (70 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (50 mL x 2) and H_2O (50 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel EtOAc (Hex = 1/1, R_f = 0.38) to afford a white crystal of desired product **14-29** (2.12 g, 69.7 % in 2 steps).

Experiment 14.17

Preparation and Analysis of Compound

Morpholine **14-30**



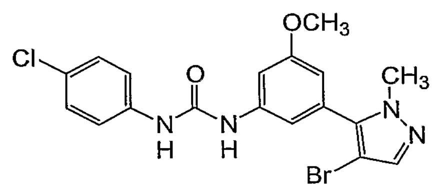
[0406] Fluorophenyl pyrazole **14-18** (509 mg, 1.69 mmol) was directly weighed into a 5 mL round-bottom flask and dissolved in DMSO (3 mL). The solution was treated with morpholine (295 µL, 3.38 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The EtOAc was washed with 1.0 N HCl (5 mL), dried

over $MgSO_4$ and concentrated under vaccum. The curde product was used for the next step without further purification. A 25 mL round-bottom flask was charged with the crude compound and $SnCl_2{\bullet}2H_2O$ (1.72 g, 6.79 mmol) and dissolved in EtOH (20 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (10 mL x 2) and H_2O (10 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, $R_f = 0.45$) to afford a white crystal of desired product **14-30** (415 mg, 73.5 % in 2 steps).

Experiment 14.18

Preparation and Analysis of Compound

Compound **158**



Typical coupling reaction of the precursors and isocyanates:

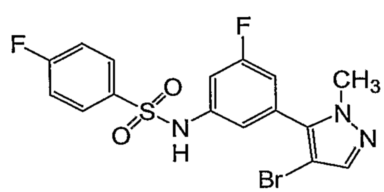
[0407] To a 1 mL oven dried vial, was aniline **14-24** (80 mg, 0.28 mmol, see Experiment **14-11** and Scheme **14-5**) dissolved in dichloroethane (0.3 mL) and treated with p-chlorophenyl isocyanate (53 mg, 0.34 mmol) at room temperature.

[0408] After stirring for 12 hrs, the solid was filtered, washed with dichloroethane (0.5 mL) and dried *in vacuo* to afford Compound **158** (90.1 mg, 75%).

Experiment 14.19

Preparation and Analysis of Compound

Compound **100**



Typical coupling reaction of the precursors and sulfonyl halides or acyl halides

[0409] To a 1 mL oven dried vial, was aniline **14-19** (50 mg, 0.17 mmol, see Experiment **14-6** and Scheme **14-3**) dissolved in dichloromethane (0.3 mL) and treated with p-fluorophenyl sulfonylchloride (40 mg, 0.20 mmol) and Et_3N (28 μL, 0.21 mmol) at 0 °C. The reaction was warmed

to room temperature and maintained for 4 hrs. The mixture was poured into H_2O (10 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/2, $R_f = 0.52$) to afford Compound **100** as a white crystal (58 mg, 85%).:

EXAMPLE 15

Experiments 15.1 – 15.22

General Synthetic Strategies, Preparation and Analysis of Compounds

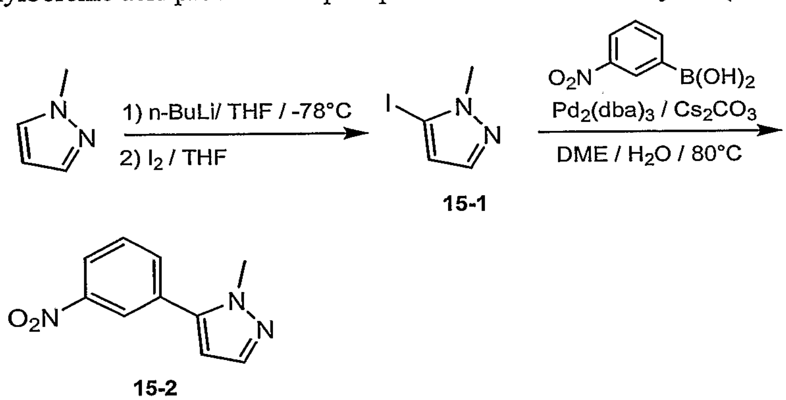
[0410] Compounds of certain embodiments of the invention were prepared according to the procedures below. The following abbreviations are employed herein:

List of Abbreviations:

DME	Dimethoxyethylene
THF	Tetrahydrofuran
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
NCS	*N*-Chlorosuccinimide
ACC	1,1-Azobis(cyclohexanecarbonitrile)
DIEA	Diisopropylethylamine
DMSO	Dimethylsulfoxide
Hex	Hexanes
EtOAc	Ethyl Acetate

GENERAL SYNTHETIC STRATEGIES

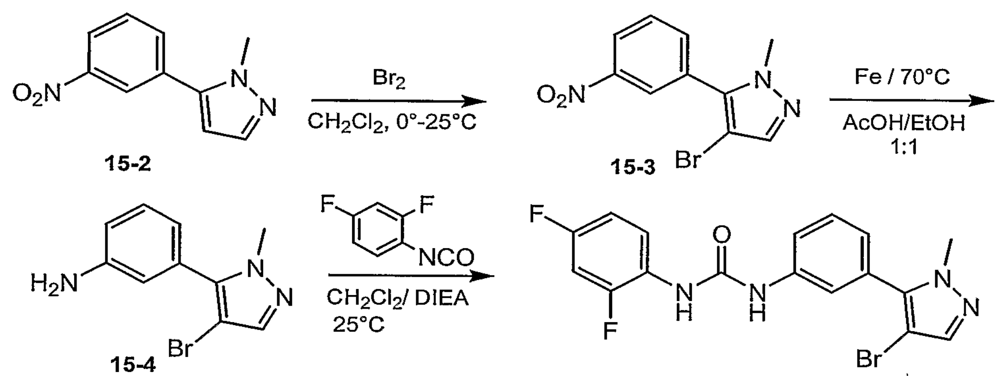
[0411] *N*-Methyl pyrazole was lithiated with n-BuLi in THF at –78°C. The lithiated pyrazole was then exchanged with I_2 to form iodopyrazole **15-1** in 78% yield. Suzuki coupling of **1** with 3-nitrophenylboronic acid provided coupled product **15-2** in 67-98% yield (Scheme **15-1**).



Scheme **15-1**

[0412] Pyrazole **15-2** was brominated at 0°C to provide **15-3** in 68% yield. Intermediate **15-3** was then reduced with iron in 1:1 acetic acid/ethanol to afford aniline **15-4** in 80% yield. Aniline **15-4** was subsequently coupled with 2,4-difluorophenylisocyanate at room temperature to provide Compound **173** in 95% yield (Method A, Scheme **15-2**).

Method A

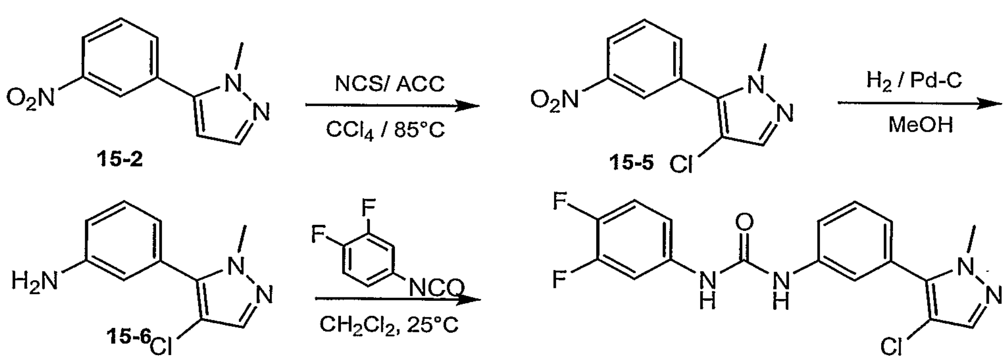


Compound **173**

Scheme **15-2**

[0413] Separately, Pyrazole **15-2** was chlorinated at 85°C with NCS providing intermediate chloropyrazole **15-5** in 87% yield. Intermediate **15-5** was then reduced with H_2/Pd-C to provide aniline **15-6** in 88% yield. Aniline **15-6** was subsequently treated with 3,4-difluorophenylisocyanate at room temperature to provide Compound **171** in 85% yield (Method B, Scheme **15-3**).

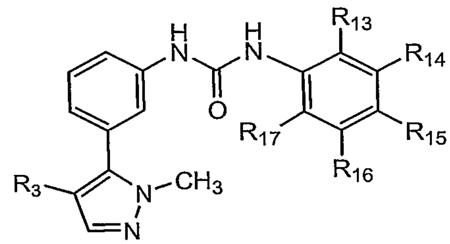
Method B



Compound **171**

Scheme **15-3**

[0414] The following compounds shown below were made in a similar manner as described above herein for Compound **173** and Compound **171**.



(X)

Compound	R_3	R_{13}	R_{14}	R_{15}	R_{16}	R_{17}	Method
Compound Name							
165	Br	H	F	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea							
166	Br	F	H	H	F	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea							
167	Br	H	F	H	F	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea							
168	Br	H	Cl	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea							
169	Br	CF_3	H	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea							
170	Br	H	CF_3	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea							
172	Cl	F	H	H	F	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea							
174	Br	F	F	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea							
175	Cl	H	F	H	F	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea							
176	Cl	H	Cl	F	H	H	B
1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea							

177	Cl	F	H	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea							
178	Cl	F	F	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea							
179	Cl	CF_3	H	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea							
180	Br	CF_3	H	Cl	H	H	A
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-phenyl)-urea							
181	Br	H	CF_3	Cl	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea							
182	Cl	H	CF_3	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea							

PREPARATION AND ANALYSIS OF COMPOUNDS

Experiment 15.1

Preparation and Analysis of Compound

5-Iodo-1-*N*-methylpyrazole **15-1**

[0415] *N*-Methylpyrazole (10.0 mL, 120.6 mmol) was dissolved in THF (250 mL) and treated with n-BuLi (75.6 mL, 120.6 mmol) at –78°C under dry N_2. The reaction was stirred for 30 min at –78°C. The reaction mixture was treated at –78°C with I_2 (30.7 gm, 120.6 mmol) in THF (200 mL). The reaction was allowed to warm to room temperature and stirred an additional 3 hours. The mixture was quenched by the addition of NH_4Cl (200 mL) stirring for 30 min. Extraction with EtOAc (3 x 100 mL) then washing of the organic phase with a 10% solution of $Na_2S_2O_3$ removed the excess I_2. The combined organic layers were then dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to provide 19.6g of 5-Iodo-1-*N*-methylpyrazole **15-1** in 78% yield (the material was used as crude in the next step): LCMS m/z 209 MH^+. ^1H NMR (400 MHz. $CDCl_3$) σ 7.46 (d, J = 2 Hz, 1H), 6.4 (d, J = 2 Hz, 1H), 3.9 (s, 3H).

Experiment 15.2

Preparation and Analysis of Compound

Pyrazole **15-2 (Route-1)**

[0416] The intermediate iodopyrazole **15-1** (588 mg, 2.82 mmol) was dissolved in DME (5 mL) and H_2O (500 µL). To this solution was added 3-nitrophenylboronic acid (943 mg, 5.65 mmol), Cs_2CO_3 (920 mg, 2.82 mmol) and $Pd(Ph_3P)_4$ (555 mg, 0.48 mmol). The mixture was degassed with argon and heated to 80°C for 12 hours. After cooling to room temperature, brine (30 mL) was added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexanes/EtOAc gradient elution) to provide 562 mg (98%) of pyrazole **15-2** as a pale yellow solid: LCMS m/z 204 MH^+. ^1H NMR (400 MHz. $CDCl_3$) σ 8.25 (s, 1H), 8.22 (dd, J=7.8, 1.0 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.64 (dd, J=8.0, 8.0 Hz, 1H), 7.52 (m, 1H), 6.39 (m, 1H), 3.92 (m, 3H).

Pyrazole **15-2 (Route-2)**

[0417] The intermediate iodopyrazole **5-1** (17.4 gm, 83.5 mmol) was dissolved in DME (200 mL) and H_2O (1 mL). To this solution was added 3-nitrophenylboronic acid (14.0 gm, 83.5 mmol), Cs_2CO_3 (27.4 gm, 83.5 mmol) and $Pd_2(dba)_3$ (1.37 gm, 14 mmol). The mixture was degassed with argon and heated to 80°C for 12 hours. After cooling to room temperature, brine (100 mL) was added and the mixture extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexanes/EtOAc gradient elution) to provide 17.1 gm (67%) of Pyrazole **15-2** as a pale yellow solid: LCMS m/z 204 MH^+. ^1H NMR (400MHz. $CDCl_3$) σ 8.25 (s, 1H), 8.22 (dd, J=7.8, 1.0 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.64 (dd, J=8.0, 8.0 Hz, 1H), 7.52 (m, 1H), 6.39 (m, 1H), 3.92 (m, 3H).

Experiment 15.3

Preparation and Analysis of Compound

Method A

Bromopyrazole **15-3**

[0418] Pyrazole **15-2** (5.79 g, 28.5 mmol) was dissolved in 150 mL of CH_2Cl_2 and cooled to 0°C. Bromine (5.40 g, 34.2 mmol) in CH_2Cl_2 (55 mL) was added drop wise under argon over 30 minutes. After the addition was complete, the reaction mixture stirred for 3 hours at room temp. The

reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and 1N NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x200 ml). The organic layers were combined, dried over Na_2SO_4, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexanes/EtOAc gradient elution) to provide 5.4 gm (68%) of Bromopyrazole **15-3** and 1.1 gm (14%) of unreacted starting material. LCMS m/z (%) = 284 (M+H^{81}Br, 100), 282 (M+H^{79}Br, 89). ^{1}H NMR (400MHz. $CDCl_3$) σ 8.33 (d, J=6.0 Hz, 1H), 8.29 (s, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.71 (dd, J=8.0 Hz, 1H), 7.56 (s, 1H), 3.87 (s, 3H).

Intermediate **15-4**:

[0419] A slurry of pyrazole **15-3** (2.05 g, 7.26 mmol) in a 1:1 mixture of acetic acid and ethanol (30 ml) was treated with iron powder (1.62 g, 29.0 mol) and heated to 70°C for 4 hours. The reaction mixture was allowed to cool to room temperature and 1N NaOH (100 ml) was added to form white precipitate (FeOH). EtOAc (100 mL) was added and filtered through celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x100 ml). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated to afford 1.46 g of **15-4**, in 80% yield as a white solid. LCMS m/z (%) = 254 (M+H^{81}Br, 100), 252 (M+H^{79}Br, 96). ^{1}H NMR (400MHz. $CDCl_3$) σ 7.50 (s, 2H), 7.26 (m, 2H), 6.75 (m, 2H), 6.68 (s, 1H), 3.81 (s, 3H).

Experiment 15.4

Preparation and Analysis of Compound

Compound **173**

[0420] Intermediate **4** (209 mg, 0.83 mmol, see Experiment **15.3**) was dissolved in 3 mL of CH_2Cl_2, treated with 2,4-difluorophenylisocyanate (385 mg, 2.49 mmol), diisopropylethylamine (168 mg, 1.66 mmol), and stirred at room temperature overnight. The solvent was removed under reduced pressure, dissolved in DMSO (5 ml), and purified by preparative HPLC to afford **Compound 173** as a white solid, 325 mg, 97% yield: LCMS m/z (%) = 409 (M+H^{81}Br, 100), 407 (M+H^{79}Br, 97). ^{1}H NMR (400 MHz. DMSO-d_6) σ 9.20 (s, 1H), 8.55 (s, 1H), 8.04 (m, 1H), 7.64 (m, 1H), 7.59 (s, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.44 (dd, J=7.8 Hz, 1H), 7.29 (m, 1H), 7.09 (d, J=7.2 Hz, 1H), 7.03 (dd, J=8.8 Hz, 1H), 3.77 (s, 3H).

Experiment 15.5

Preparation and Analysis of Compound

Compound **165**

[0421] Intermediate **4** was treated with 3,4-difluorophenylisocyanate, in a similar manner to Compound **173**, providing a 99% yield of Compound **165**: LCMS m/z (%) = 409 (M+H^{81}Br, 100), 407 (M+H^{79}Br, 97). ^{1}H NMR (400 MHz. DMSO-d$_6$) σ 8.98 (s, 2H), 7.57 (m, 3H), 7.44 (dd, J=8.0 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 7.31 (d, J=9.6 Hz, 1H), 7.10 (m, 2H), 3.78 (s, 3H).

Experiment 15.6

Preparation and Analysis of Compound

Compound **166**

[0422] Intermediate **4** was treated with 2,5-difluorophenylisocyanate, in a similar manner to Compound **173**, providing a 76% yield of Compound **166**: LCMS m/z (%) = 409 (M+H^{81}Br, 100), 407 (M+H^{79}Br, 97). ^{1}H NMR (400 MHz. CDCL$_3$) σ 7.93 (m, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.57 (s, 1H), 7.50 (s, 1H), 7.24 (m, 2H), 7.10 (d, J=6.8 Hz, 1H), 6.96 (m, 1H), 6.64 (m, 1H), 3.82 (s, 3H).

Experiment 15.7

Preparation and Analysis of Compound

Compound **167**

[0423] Intermediate **4** was treated with 3,5-difluorophenylisocyanate, in a similar manner to Compound **173**, after chromatography on silica (Chromatatron, Hex/EtOAc gradient), providing a 45% yield of Compound **167**: LCMS m/z (%) = 409 (M+H^{81}Br, 100), 407 (M+H^{79}Br, 96). ^{1}H NMR (400 MHz. Acetone- d$_6$) σ 8.59 (s, 1H), 8.47 (s, 1H), 7.68 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.52 (s, 1H), 7.47 (dd, J=7.8 Hz, 1H), 7.24 (J=9.6 Hz, 2H), 7.14 (d, J=7.6 Hz, 1H), 6.61 (dd, J=8.6 Hz, 1H), 3.83 (s, 3H).

Experiment 15.8

Preparation and Analysis of Compound

Compound **168**

[0424] Intermediate **4** was treated with 3-chloro-4-fluorophenylisocyanate, in a similar manner to Compound **173**, providing a 91% yield of Compound **168**: LCMS m/z (%) = 427 (M+H^{81}Br, ^{37}Cl, 33), 425 (M+H^{81}Br, ^{35}Cl & ^{79}Br, ^{37}Cl, 100), 423 (M+H^{79}Br, ^{35}Cl, 63). ^{1}H NMR (400

MHz. Acetone- d_6) σ 8.41 (s,1H), 8.37 (s, 1H), 7.87 (m,1H),7.69 (m, 1H), 7.62 (d, J=2.4 Hz, 1H), 7.52 (s, 1H), 7.45 (dd, J=7.8 Hz, 1H), 7.38 (m, 1H), 7.21 (dd, J=9.0 Hz, 1H), 7.12 (d, J=6.8 Hz, 1H), 3.83 (s, 3H).

Experiment 15.9

Preparation and Analysis of Compound

Compound **169**

[0425] Intermediate **4** was treated with 2-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound **173**, providing a 47% yield of Compound **169**: LCMS m/z (%) = 459 ($M+H^{81}Br$, 100), 457 ($M+H^{79}Br$, 78). ^1H NMR (400 MHz. DMSO-d_6) σ 9.47 (s, 1H), 8.64 (s, 1H), 8.16 (s, 1H), 7.86 (m, 1H), 7.76 (m, 1H), 7.64 (s, 1H), 7.54 (m, 2H), 7.45 (dd, J=7.8 Hz, 1H), 7.09 (d, J=7.2 Hz, 1H), 3.77 (s, 3H).

Experiment 15.10

Preparation and Analysis of Compound

Compound **170**

[0426] Intermediate **4** was treated with 3-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound **173**, providing a 56% yield of Compound **170**: LCMS m/z (%) = 459 ($M+H^{81}Br$, 100), 457 ($M+H^{79}Br$, 82). ^1H NMR (400 MHz. DMSO-d_6) σ 9.13 (s, 1H), 9.04 (s, 1H), 7.98 (m, 1H), 7.64 (m, 2H), 7.58 (s, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.45 (m, 2H), 7.09 (d, J=8.8 Hz, 1H), 3.77 (s, 3H).

Experiment 15.11

Preparation and Analysis of Compound

Compound **174**

[0427] Intermediate **4** was treated with 2,3,4-trifluorophenylisocyanate, in a similar manner to Compound **173**, providing a 22% yield of Compound **174**: LCMS m/z (%) = 427 ($M+H^{81}Br$, 100), 425 ($M+H^{79}Br$, 78). ^1H NMR (400 MHz. Acetone- d_6) σ 8.74 (s, 1H), 8.22 (s, 1H), 8.01 (m, 1H), 7.71 (m, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.52 (s, 1H), 7.48 (dd, J=7.8 Hz, 1H), 7.15 (m, 2H), 3.84 (s, 3H).

Experiment 15.12

Preparation and Analysis of Compound

Compound **180**

[0428] Intermediate **4** was treated with 2-trifluoromethyl-4-chlorophenylisocyanate, in a similar manner to Compound **173**, after chromatography on silica (Biotage, Hex/EtOAc gradient) provided Compound **180** in a 73% yield: LCMS m/z (%) = 477 (M+H^{81}Br, ^{37}Cl, 40), 475 (M+H^{81}Br, ^{35}Cl & ^{79}Br, ^{37}Cl, 100), 473 (M+H^{79}Br, ^{35}Cl, 72). ^{1}H NMR (400 MHz. Acetone-d_6) σ 9.04 (s, 1H), 8.19 (d, J=9.2 Hz, 1H), 7.77 (s, 1H), 7.66 (m, 4H), 7.52 (s, 1H), 7.48 (dd, J=8.0 Hz, 1H), 7.14 (d, J=7.6, 1H), 3.83 (s, 3H).

Experiment 15.13

Preparation and Analysis of Compound

Compound **181**

[0429] Intermediate **4** was treated with 3-trifluoromethyl-4-chlorophenylisocyanate, in a similar manner to Compound **173**, providing a 56% yield of Compound **181**: LCMS m/z (%) = 477 (M+H^{81}Br, ^{37}Cl, 34), 475 (M+H^{81}Br, ^{35}Cl & ^{79}Br, ^{37}Cl, 100), 473 (M+H^{79}Br, ^{35}Cl, 62). ^{1}H NMR (400 MHz. Acetone-d_6) σ 8.85 (s, 1H), 8.72 (s, 1H), 8.16 (d, J=2.8 Hz, 1H), 7.77 (s, J=8.8Hz, 1H), 7.71 (s, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.52 (s, 1H), 7.48 (dd, J=7.8 Hz, 1H), 7.14 (d, J=8.8, 1H), 3.84 (s, 3H).

Experiment 15.14

Preparation and Analysis of Compound

Method B:

Chloropyrazole **15-5**

[0430] Pyrazole **15-2** (2.51 g, 12.3 mmol) was dissolved in 70 ml of CCl_4 and heated to 85°C under reflux. *N*-Chlorosuccinimide (1.81 g, 13.6 mmol) and 1,1-Azobis (cyclohexanecarbonitrile) were added and stirred overnight. The reaction mixture was allowed to cool to room temperature then to 0°C and the white precipitate filtered off. The solvent was removed under reduced pressure and purified by flash chromatography (SiO_2, Hexanes/EtOAc gradient elution) to provide 2.54 g, 87% yield of chloropyrazole **15-5**. LCMS m/z (%) = 240 (M+H^{37}Cl, 54), 238 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. $CDCl_3$) σ 8.33 (d, J=8.4 Hz, 1H), 8.31 (s, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.72 (dd, J=7.8 Hz, 1H), 7.55 (s, 1H), 3.87 (s, 3H).

Intermediate **15-6**:

[0431] A slurry of the chloropyrazole **15-5** (973 mg, 4.09 mmol) was reduced at 55 psi H_2 / Pd-C for 4 hours to provide 749 mg of intermediate **15-6** in 88% yield. LCMS m/z (%) = 210 (M+H^{37}Cl, 68), 208 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. $CDCl_3$) σ 7.47 (s, 2H), 7.29 (s, 1H), 7.25 (dd, J=3.8 Hz, 1H), 6.77 (d, J=2.0 Hz, 1H), 6.75 (d, J=2.0 Hz, 1H), 6.7 (m, 1H), 3.81 (s, 3H).

Experiment 15.15

Preparation and Analysis of Compound

Compound **171**

[0432] Intermediate **15-6** (200 mg, 0.96 mmol) was dissolved in 3 mL of CH_2Cl_2, treated with 3,4-difluorophenylisocyanate (4.49 mg, 2.89 mmol), diisopropylethylamine (194 mg, 1.92 mmol), and stirred at room temperature overnight. The solvent was removed under reduced pressure, dissolved in DMSO (5 ml), and purified by preparative HPLC to afford Compound **171** as a white solid, 298 mg, 85% yield: LCMS m/z (%) = 365 (M+H^{37}Cl, 27), 363 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. DMSO-d_6) σ 8.95 (m, 2H), 7.62 (m, 3H), 7.52 (d, J=8.0 Hz, 1H), 7.45 (dd, J=7.8 Hz, 1H), 7.32 (m, 1H), 7.10 (m, 2H), 3.77 (s, 3H).

Experiment 15.16

Preparation and Analysis of Compound

Compound **172**

[0433] Intermediate **6** was treated with 2,5-difluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 57% yield of Compound **172**: LCMS m/z (%) = 365 (M+H^{37}Cl, 32), 363 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. CD_3OD) σ 7.99 (m, 1H), 7.63 (s, 1H), 7.49 (m, 2H), 7.44 (dd, J=8.0 Hz, 1H), 7.10 (m, 3H), 6.69 (m, 2H), 3.81 (s, 3H).

Experiment 15.17

Preparation and Analysis of Compound

Compound **175**

[0434] Intermediate **6** was treated with 3,5-difluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 20% yield of Compound **175**: LCMS m/z (%) = 365 (M+H^{37}Cl, 27), 363 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz.

$CDCl_3$) σ 7.50 (s, 1H), 7.44 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.25 (s, 2H), 7.14 (m, 1H), 6.98 (d, J=6.8 Hz, 2H), 6.49 (m, 1H), 3.82 (s, 3H).

Experiment 15.18

Preparation and Analysis of Compound

Compound **176**

[0435] Intermediate **6** was treated with 3-chloro-4-fluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 21% yield of Compound **176**: LCMS m/z (%) = 383 (M+H^{37}Cl,^{37}Cl, 19), 381 (M+H^{37}Cl,^{35}Cl, 73), 379 (M+H^{35}Cl,^{35}Cl, 100). ^{1}H NMR (400 MHz. $CDCl_3$) σ 7.50 (m, 2H), 7.43 (m, 2H), 7.25 (s, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 7.06 (dd, J=8.6 Hz, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 3.82 (s, 3H).

Experiment 15.19

Preparation and Analysis of Compound

Compound **177**

[0436] Intermediate **6** was treated with 2,4-difluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 37% yield of Compound **177**: LCMS m/z (%) = 365 (M+H^{37}Cl, 32), 363 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. DMSO-d_6) σ 9.20 (s, 1H), 8.55 (s, 1H), 8.04 (m, 1H), 7.64 (s, 1H), 7.59(s, 1H), 7.50 (d, J=5.6 Hz, 1H), 7.44 (dd, J=7.8, 1H), 7.29 (m, 1H), 7.09 (d, J=6.0, 1H), 7.03 (dd, J=8.8, 1H), 3.77 (s, 3H).

Experiment 15.20

Preparation and Analysis of Compound

Compound **178**

[0437] Intermediate **6** was treated with 2,3,4-trifluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 45% yield of Compound **178**: LCMS m/z (%) = 383 (M+H^{37}Cl, 52), 381 (M+H^{35}Cl, 100). ^{1}H NMR (400 MHz. Acetone-d_6) σ 8.68 (s, 1H), 8.17 (s, 1H), 8.02 (m, 2H), 7.72 (s, 1H), 7.63 (d, J=7.2 Hz, 1H), 7.51 (s, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.16 (m, 1H), 3.83 (s, 3H).

Experiment 15.21

Preparation and Analysis of Compound

Compound **179**

[0438] Intermediate **6** was treated with 2-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound **171**, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 32% yield of Compound **179**: LCMS (%) = 415 ($M+H^{37}Cl$, 48), 413 ($M+H^{35}Cl$, 100). ^1H NMR (400 MHz. Acetone-d_6) σ 8.92 (s, 1H), 8.15 (s, 1H), 8.07 (dd, J=6.8 Hz, 1H), 7.96 (m, 1H), 7.72 (m, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.49 (m, 3H), 7.14 (d, J=7.6 Hz, 1H), 3.82 (s, 3H).

Experiment 15.22

Preparation and Analysis of Compound

Compound **182**

[0439] Intermediate **4** was treated with 3-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound **171**, providing a 71% yield of Compound **182**: LCMS m/z (%) = 415 ($M+H^{37}Cl$, 79), 413 ($M+H^{35}Cl$, 100). ^1H NMR (400 MHz. Acetone-d_6) σ 8.50 (s, 1H), 8.45 (s, 1H), 8.04 (d, J=8.8 Hz, 1H), 7.76 (m, 1H), 7.71 (s, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.51 (s, 1H), 7.48 (dd, J=7.8 Hz, 1H), 7.33 (dd, J=9.6 Hz, 1H), 7.15 (d, J=7.2 Hz, 1H), 3.83 (s, 3H).

EXAMPLE 16

Experiments 16.1 – 16.5

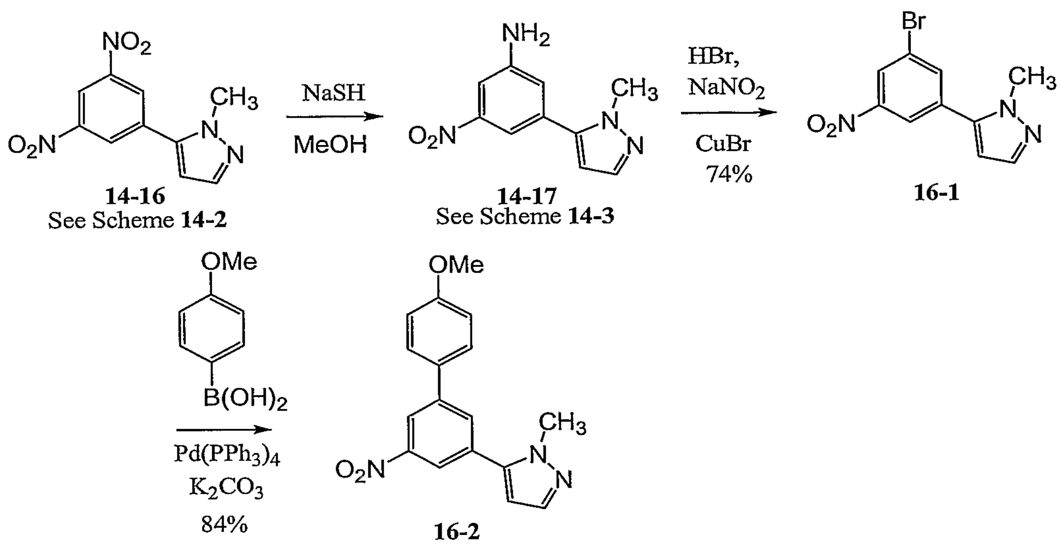
General Synthetic Strategies, Preparation and Analysis of Compounds

[0440] Compounds of certain embodiments of the invention were prepared according to the procedures below.

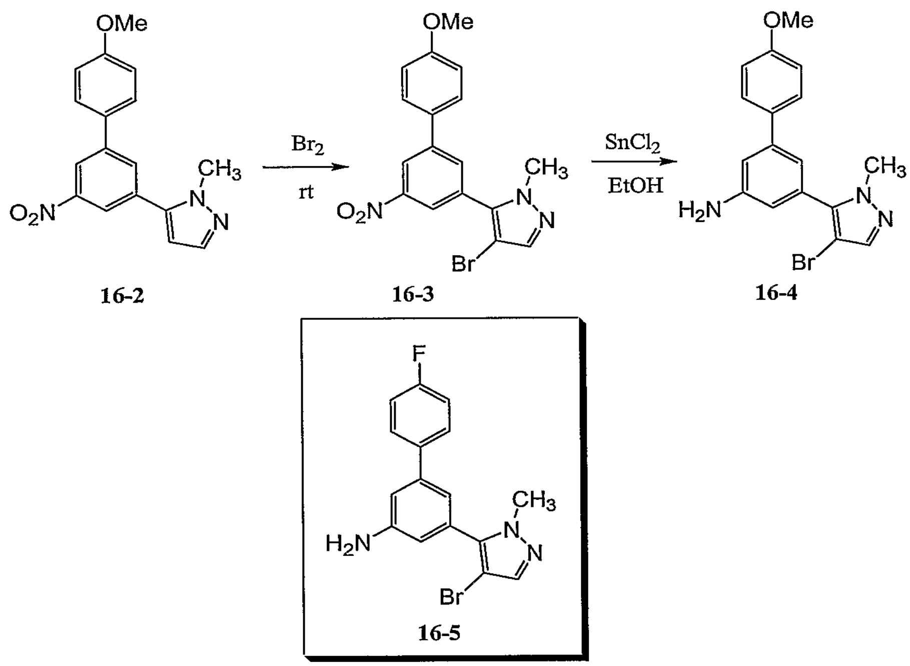
General Synthetic Strategies

[0441] Various aryl functionalities were introduced on the phenyl ring. By way of example, dinitro **14-15** (see Scheme**14-2**) was reduced with NaSH in ethanol under reflux conditions, followed by bromination under Sandmyer's conditions to afford Aryl bromide **16-1** in 56 % yield (2 steps). Aryl bromide **16-1** was coupled with *p*-methoxyphenyl boronic acid with $Pd(PPh_3)_4$ and K_2CO_3 as a base in dioxane to furnish the coupled product **16-2** (Scheme **16-1**). The reaction was very clean and the desired product was purified by recrystallization in ethanol. Coupled product **16-2** was subsequently brominated with Br_2 in dichloromethane at room temperature (i.e., **16-3**) followed by

reduction with $SnCl_2 \bullet 2H_2O$ in Ethanol to furnish the aniline precursor **16-4**. 4-Fluorophenyl functionality was also introduced on the ring in a similar manner (Scheme **16-2**).



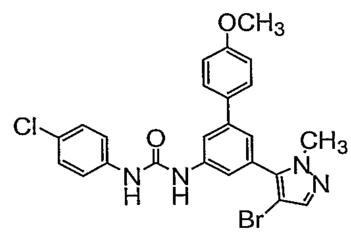
Scheme **16-1**



Scheme **16-2**

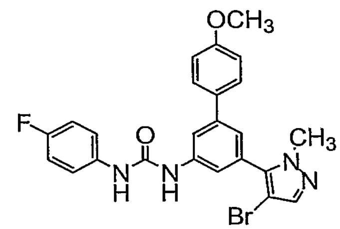
[0442] Anilines **16-4** and **16-5** were coupled with various isocyanates, acyl halides and sulfonyl halides to form urea, amide and sulfonamide type molecules respectively in good yields. The tables of the new compounds are shown below (**TABLES 16-1** and **16-2**).

TABLE 16-1 Compounds of the invention containing *p*-methoxyphenyl functionality.



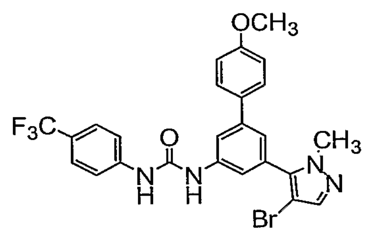
Compound **191**

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea



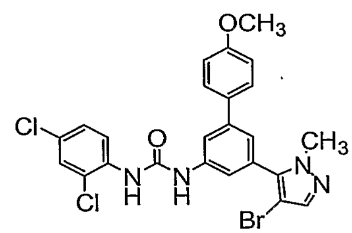
Compound **192**

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea



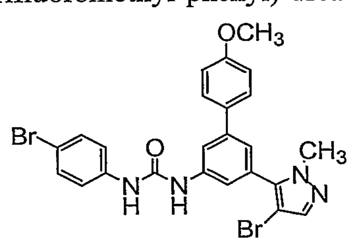
Compound **186**

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea



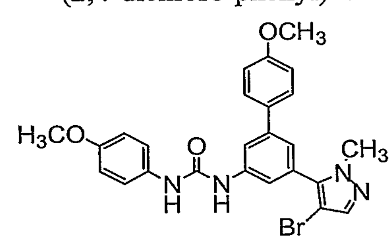
Compound **187**

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea



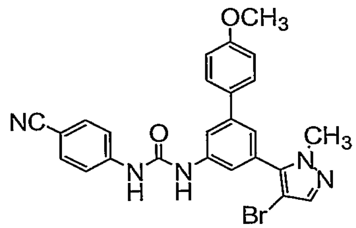
Compound **200**

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea

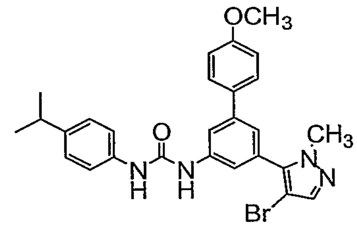


Compound **198**

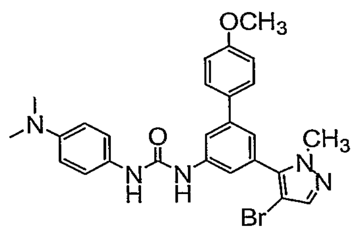
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea



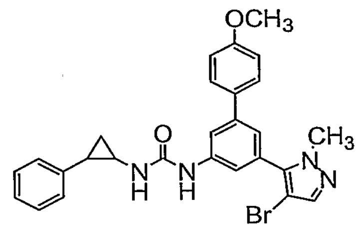
Compound **196**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea



Compound **201**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea

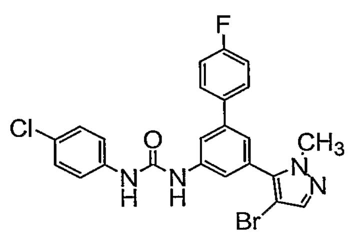


Compound **185**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea

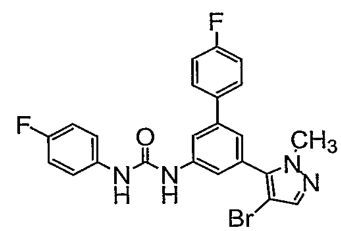


Compound **202**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea

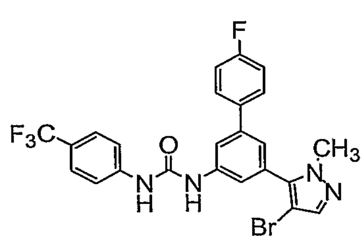
TABLE 16-1 Compounds of the invention containing *p*-fluorophenyl functionality.



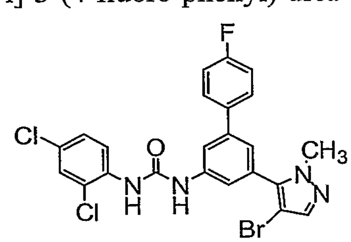
Compound **199**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea



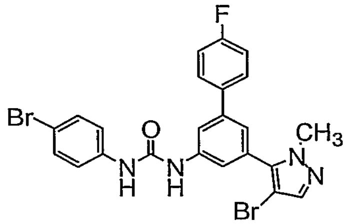
Compound **204**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea



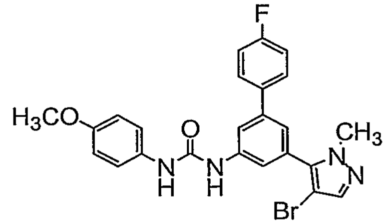
Compound **190**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea



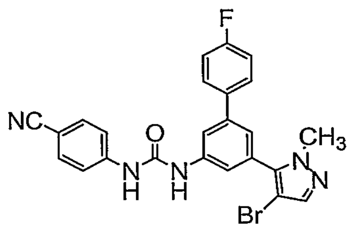
Compound **194**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea



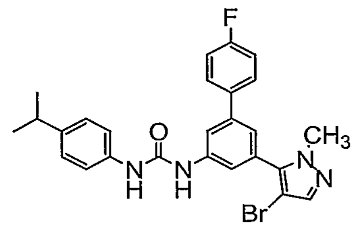
Compound **197**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea



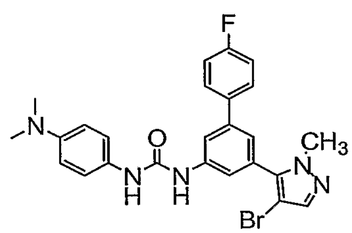
Compound **188**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea



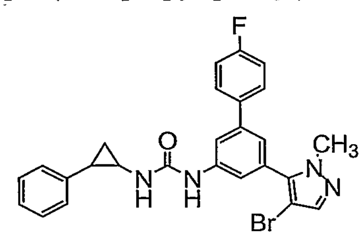
Compound **193**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea



Compound **195**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea



Compound **189**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea

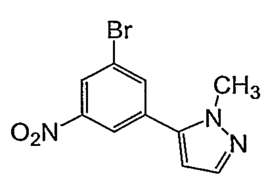


Compound **203**
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea

Experiment 16.1

Preparation and Analysis of Compound

Aryl bromide **16-1:**



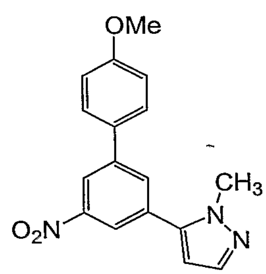
[0443] **Aniline 14-17** (9.89 g, 39.9 mmol, Experiment **14.4** and Scheme **14-3**) was dissolved in MeOH (150 mL) and toluene (50 mL) and refluxed to dissolve all solids. NaSH (6.0 g, 107.7

mmol) in MeOH (50 mL) was added into the solution for 45 min. The reaction mixture was stirred for 30 min at the same temperature and cooled to room temperature. The reaction mixture was concentrated under vaccum and dissolved in EtOAc (250 mL). The EtOAc was washed with H_2O (100 mL x 2), dried over $MgSO_4$ and concentrated to afford crude Aniline **14-17**. The crude compound was used for the next step without further purification. The crude Aniline **14-17** was added into 45% HBr (50 mL) at 0 °C and warmed to room temperature. After stirring for 30 min, the solution was cooled to –30 °C and $NaNO_2$ (2.75 g, 39.9 mmol) added portionwise for 10 min. The reaction mixture was maintained at the same temperature for 30 min. The mixture was heated to 100 °C and stirred for 10 min. The reaction mixture was cooled to room temperature and quenched with crushed ice (250 g). The crude product was extracted with EtOAc (250 mL), dried over $MgSO_4$ and concentrated under vaccum. The crude material was purified by column chromatograph (EtOAc/Hex = 1/1, R_f = 0.85) to afford the desired product as a white crystal Aryl bromide **16-1** (5.8 g, 52.1 % in 2 steps).

Experiment 16.2

Preparation and Analysis of Compound

Biaryl **16-2:**

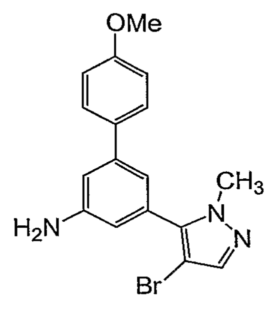


[0444] Aryl bromide **16-1** (700 mg, 2.5 mmol), *p*-methoxyphenyl boronic acid (380 mg, 2.5 mmol) and $Pd(PPh_3)_4$ (289 mg, 0.25mmol) were directly weighed into a 25 mL round-bottom flask and dissolved in dioxane (10 mL). The solution was treated with K_2CO_3 (760 mg, 5.5 mmol) in H_2O (2.75 mL) and heated to 80 °C. After stirring for 4 hrs, the reaction was poured into H_2O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The residue was purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.64) to afford Biaryl **16-2** as a white crystal (649 mg, 84.2%).:

Experiment 16.3

Preparation and Analysis of Compound

Amino biaryl **16-4:**

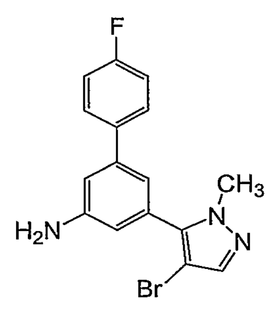


[0445] To the solution of Biaryl **16-2** (618 mg, 2.0 mmol) in dichloromethane (5 mL), was added dropwise Br_2 (128 μL, 2.5 mmol) in dichloromethane (1 mL) for 5 min at 0 °C. After addition of Br_2, the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H_2O (10 mL), concentrated under vacuum and triturated in EtOH to afford yellowish crystals. A 5 mL round-bottom flask was charged with the solids and $SnCl_2•2H_2O$ (2.61 g, 10.0 mmol) and dissolved in EtOH (5 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.25) to afford the desire Amino biaryl **16-4** as white crystals (583 mg, 82% in 2 steps).

Experiment 16.4

Preparation and Analysis of Compound

Amino biaryl **16-5:**



[0446] Aryl bromide **16-1** (1.28 g, 4.57 mmol), *p*-fluorophenyl boronic acid (700 mg, 5.0 mmol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol) were directly weighed into a 50 mL round-bottom flask and dissolved in dioxane (30 mL). The solution was treated with K_2CO_3 (1.38 g, 10.0 mmol) in H_2O (5.43 mL) and heated to 80 °C. After stirring for 4 hrs, the reaction was poured into H_2O (50 mL) and

extracted with EtOAc (30 mL x 2). The EtOAc was dried over $MgSO_4$ and concentrated under vaccum. The residue was dissolved in dichloromethane (25 mL), and Br_2 (282 µL, 5.5 mmol) in dichloromethane (3 mL) was added dropwise for 5 min at 0 °C. After addition of Br_2, the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H_2O (20 mL), concentrated under vaccum and triturated in EtOH to afford yellowish crystals. A 5 mL round-bottom flask was charged with the solids and $SnCl_2 \cdot 2H_2O$ (4.12 g, 18.3 mmol) and dissolved in EtOH (20 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vaccum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over $MgSO_4$, concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.31) to afford Amino biaryl **16-5** as white crystals (1.31 g, 83 % in 3 steps).

[0447] In general, the coupling procedures disclosed herein between an amine, such as, Amino biaryls **16-5**, **16-5** and the like, with isocyanates, acid halides and sulfonyl halides can be utilized to achieve the desired urea, amide or sulfonamide products respectively. Analytical data for certain representative compounds, such as those compounds in **TABLES 16-1** and **16-2**, can be seen in **TABLE 16-3** below:

TABLE 16-3
Analytical Data for Representative Compounds of the Invention

Compound No.	**Expected**	**Found** (M+H^{79}Br)	**Found** (M+H^{81}Br)
185	520	520	522
186	545	545	547
187	545	545	547
191	511	511	513
192	495	495	497
196	502	502	504
198	507	507	509
200	557	557	559
201	519	519	521
202	517	517	519

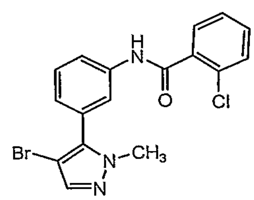
[0448] An important point that can be derived from the foregoing data is that by using a constitutively activated form of the receptor in the direct identification of candidate compounds, the selectivity of the compounds is exceptional: as those in the art appreciate, the homology between the human 5-HT_{2A} and 5-HT_{2C} receptors is about 95%, and even with such homology, certain of the directly identified compounds, e.g., Compounds **8** and **9** evidence a 100-fold difference in selectivity preference (as measured by IC_{50} values) for the 5-HT_{2A} receptor compared with the 5-HT_{2C} receptor.

This is important for pharmaceutical compositions in that such selectivity can help to reduce side-effects associated with interaction of a drug with a non-target receptor.

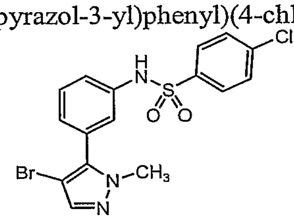
[0449] Different embodiments of the invention will consist of different constitutively activated receptors, different expression systems, different assays, and different compounds. Those skilled in the art will understand which receptors to use with which expression systems and assay methods. All are considered within the scope of the teaching of this invention.

[0450] In some embodiments of each of the genera disclosed in this specification, the following compounds (a) through (k), and combinations or subcombinations thereof, are included therein:

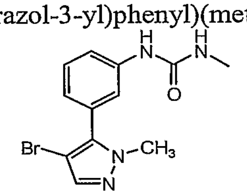
(a) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-chlorophenyl)carboxamide;



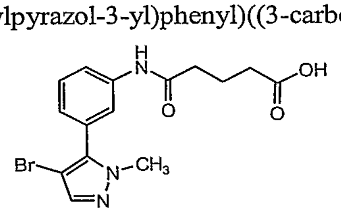
(b) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl)sulfonamide;



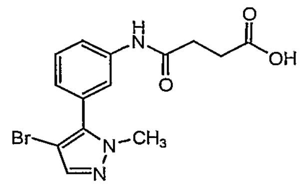
(c) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(methylamino)carboxamide;



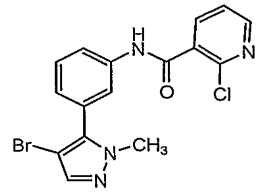
(d) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((3-carboxy-prop-1-yl)carboxamide;



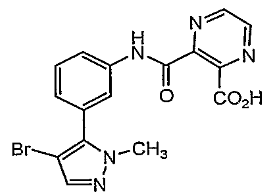
(e) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-carboxy-eth-1-yl)carboxamide;



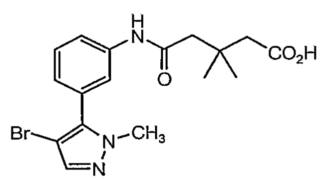
(f) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-chloro-3-pyridyl)carboxamide;



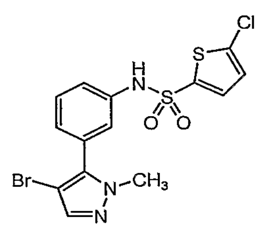
(g) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((3-carboxy-pyrazin-2-yl)carboxamide;



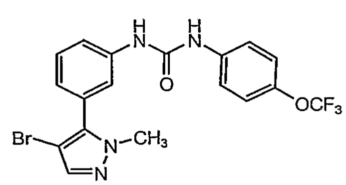
(h) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-methyl-1-carboxy-prop-2-yl)carboxamide;



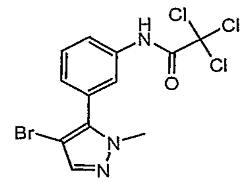
(i) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((5-chlorothiophen-2-yl)sulfonamide;



(j) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl) amino) carboxamide;



(k) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(trichloromethyl)carboxamide.



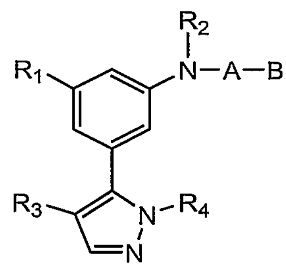
[0451] In some embodiments of each of the general disclosed in this specification, compounds (a) through (k) above, and combinations or subcombinations thereof, are not included therein.

[0452] Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety. :

CLAIMS

We claim:

1. A compound of Formula (**I**):



(**I**)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

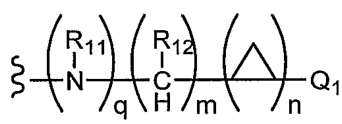
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



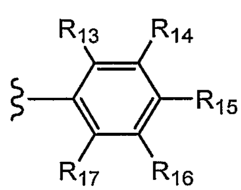
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10},

NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or
a pharmaceutically acceptable salt.

2. The compound of claim 1 wherein B is L_1, q is 1, m is 0, and n is 0.

3. The compound of claim 1 wherein B is L_1, q is 1, m is 1, and n is 0.

4. The compound of claim 1 wherein B is L_1, q is 1, m is 0, and n is 1.

5. The compound of claim 1 wherein B is L_1, q is 0, m is 0, and n is 0.

6. The compound of claim 1 wherein B is L_2.

7. The compound of claim 2 wherein A is C(=O).

8. The compound of claim 3 wherein A is C(=O).

9. The compound of claim 4 wherein A is C(=O).

10. The compound of claim 5 wherein A is C(=O).

11. The compound of claim 2 wherein A is C(=S).

12. The compound of claim 3 wherein A is C(=S).

13. The compound of claim 4 wherein A is C(=S).

14. The compound of claim 5 wherein A is C(=S).

15. The compound of claim 5 wherein A is SO_2.

16. The compound of claim 1 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

17. The compound of claim 1 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

18. The compound of claim 7 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

19. The compound of claim 7 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

20. The compound of claim 8 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

21. The compound of claim 8 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

22. The compound of claim 9 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

23. The compound of claim 9 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

24. The compound of claim 1 wherein R_2 is H and R_4 is methyl.

25. The compound of claim 16 wherein R_2 is H and R_4 is methyl.

26. The compound of claim 17 wherein R_2 is H and R_4 is methyl.

27. The compound of claim 18 wherein R_2 is H and R_4 is methyl.

28. The compound of claim 19 wherein R_2 is H and R_4 is methyl.

29. The compound of claim 20 wherein R_2 is H and R_4 is methyl.

30. The compound of claim 21 wherein R_2 is H and R_4 is methyl.

31. The compound of claim 22 wherein R_2 is H and R_4 is methyl.

32. The compound of claim 23 wherein R_2 is H and R_4 is methyl.

33. The compound of any of claims 25 through 32 wherein R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2.

34. The compound of claim 15 wherein R_2 is H and R_4 is methyl.

35. The compound of claim 34 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

36. The compound of claim 6 wherein A is (C=O).

37. The compound of claim 36 wherein R_4 is methyl.

38. The compound of claim 37 wherein R_2 is H.

39. The compound of claim 38 wherein Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl, butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-methoxyphenyl, 2-chlorophenyl, $-C(CH_3)=CH$, 1-(N-pyridyl)ethyl, or 9-fluoreneylmethyl.

40. The compound of claim 39 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3; and R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

41. A compound of claim 1 selected from the group consisting of

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;
4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester;

5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid methyl ester;

1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-phenyl)-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea;

5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea;

1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea;

1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea;

1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-trifluoromethoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-thiourea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluoro-benzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea;

1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-benzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea
and
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea.

42. A compound of claim 1 selected from the group consisting of:
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;
1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-phenyl)-urea;
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea
and
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea.

43. The compound of claim 1 selected from the group consisting of:
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy)phenyl)amino)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy) phenyl)methyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)-carboxamide;

N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;

N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethylthio)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;

2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-dimethoxyphenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-trimethoxyphenylmethyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl) amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenylmethyl)carboxamide

and

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide.

44. The compound of claim 1 selected from the group consisting of:

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-urea;

1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea;

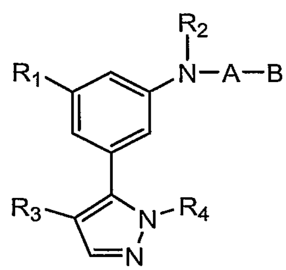
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-phenyl)-urea;

3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea;

3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea

and 3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea.

45. A compound of Formula (**I**):



(**I**)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

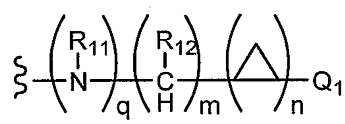
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



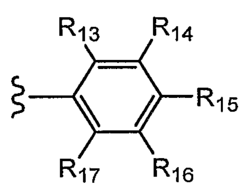
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl,

alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is –O-Q_2 wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, -C(p)$_3$, or -O-C(p)$_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt; provided that the compound is not any of the following 43 compounds:

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy) phenyl)amino)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy) phenyl)methyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)-carboxamide;

N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;

N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethylthio)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;

2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-dimethoxyphenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-trimethoxyphenylmethyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl) amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenylmethyl)carboxamide

and

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide.

46. The compound of claim 45 wherein B is L_1, q is 1, m is 0, and n is 0.

47. The compound of claim 45 wherein B is L_1, q is 1, m is 1, and n is 0.

48. The compound of claim 45 wherein B is L_1, q is 1, m is 0, and n is 1.

49. The compound of claim 45 wherein B is L_1, q is 0, m is 0, and n is 0.

50. The compound of claim 45 wherein B is L_2.

51. The compound of claim 46 wherein A is C(=O.

52. The compound of claim 47 wherein A is C(=O).

53. The compound of claim 48 wherein A is C(=O).

54. The compound of claim 49 wherein A is C(=O).

55. The compound of claim 46 wherein A is C(=S).

56. The compound of claim 47 wherein A is C(=S).

57. The compound of claim 48 wherein A is C(=S).

58. The compound of claim 49 wherein A is C(=S).

59. The compound of claim 49 wherein A is SO_2.

60. The compound of claim 45 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

61. The compound of claim 45 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

62. The compound of claim 51 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

63. The compound of claim 51 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

64. The compound of claim 52 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

65. The compound of claim 52 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

66. The compound of claim 53 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3.

67. The compound of claim 53 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

68. The compound of claim 45 wherein R_2 is H and R_4 is methyl.

69. The compound of claim 60 wherein R_2 is H and R_4 is methyl.

70. The compound of claim 61 wherein R_2 is H and R_4 is methyl.

71. The compound of claim 62 wherein $R_2$is H and R_4 is methyl.

72. The compound of claim 63 wherein R_2 is H and R_4 is methyl.

73. The compound of claim 64 wherein R_2 is H and R_4 is methyl.

74. The compound of claim 65 wherein R_2 is H and R_4 is methyl.

75. The compound of claim 66 wherein R_2 is H and R_4 is methyl.

76. The compound of claim 67 wherein R_2 is H and R_4 is methyl.

77. The compound of any of claims 69 through 76 wherein R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2.

78. The compound of claim 59 wherein R_2 is H and R_4 is methyl.

79. The compound of claim 78 wherein R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

80. The compound of claim 50 wherein A is (C=O).

81. The compound of claim 80 wherein R_4 is methyl.

82. The compound of claim 81 wherein R_2 is H.

83. The compound of claim 82 wherein Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl, butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-methoxyphenyl, 2-chlorophenyl, -$C(CH_3)$=CH, 1-(N-pyridyl)ethyl, or 9-fluoreneylmethyl.

84. The compound of claim 83 wherein R_1 is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH_3; and R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

85. A compound of claim 45 selected from the group consisting of:

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;
4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea;
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester;

5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid methyl ester;

1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-phenyl)-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-phenyl}-urea;

1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea;

5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea;

1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea;

1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea;

1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-trifluoromethoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-thiourea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluoro-benzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea;

1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-benzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea and

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea.

86. A compound of claim 45 selected from the group consiting of:

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;

1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea;

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea

and

1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea.

87. A compound of claim 45 selected from the group consisting of:

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-urea;

1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;

3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-phenyl)-urea;

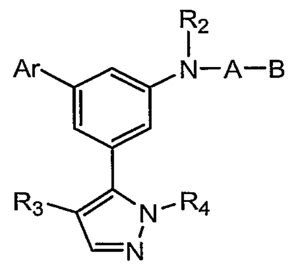
3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea;

3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea

and

3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea.

88. A compound of Formula (**XV**):



(XV)

wherein:

i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR_7, OH, NR_8R_9, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl $-C(p)_3$, or $-O-C(p)_3$ where p is halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl; or

R_8 and R_9 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_7 is H or C_{1-6} alkyl;

R_{10} is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

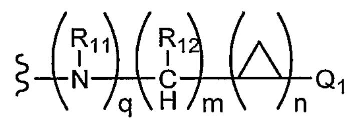
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



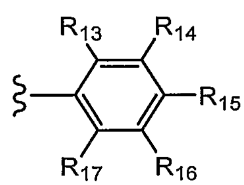
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt.

89. The compound of claim 88 wherein B is L_1, q is 1, m is 0, and n is 0.

90. The compound of claim 88 wherein B is L_1, q is 1, m is 1, and n is 0.

91. The compound of claim 88 wherein B is L_1, q is 1, m is 0, and n is 1.

92. The compound of claim 88 wherein B is L_1, q is 0, m is 0, and n is 0.

93. The compound of claim 88 wherein B is L_2.

94. The compound of claim 89 wherein A is C(=O).

95. The compound of claim 90 wherein A is C(=O).

96. The compound of claim 91 wherein A is C(=O).

97. The compound of claim 92 wherein A is C(=O).

98. The compound of claim 89 wherein A is C(=S).

99. The compound of claim 90 wherein A is C(=S).

100. The compound of claim 91 wherein A is C(=S).

101. The compound of claim 92 wherein A is C(=S).

102. The compound of claim 92 wherein A is SO_2.

103. The compound of claim 88 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.

104. The compound of claim 88 wherein R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

105. The compound of claim 94 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.

106. The compound of claim 94 wherein R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

107. The compound of claim 95 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.

108. The compound of claim 95 wherein R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

109. The compound of claim 96 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.

110. The compound of claim 96 wherein R_3 is Cl, Br, I, -$COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

111. The compound of claim 88 wherein R_2 is H and R_4 is methyl.

112. The compound of claim 103 wherein R_2 is H and R_4 is methyl.

113. The compound of claim 104 wherein R_2 is H and R_4 is methyl.

114. The compound of claim 105 wherein $R_2$is H and R_4 is methyl.

115. The compound of claim 106 wherein R_2 is H and R_4 is methyl.

116. The compound of claim 107 wherein R_2 is H and R_4 is methyl.

117. The compound of claim 108 wherein R_2 is H and R_4 is methyl.

118. The compound of claim 109 wherein R_2 is H and R_4 is methyl.

119. The compound of claim 110 wherein R_2 is H and R_4 is methyl.

120. The compound of any of claims 112 through 119 wherein R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2.

121. The compound of claim 102 wherein R_2 is H and R_4 is methyl.

122. The compound of claim 121 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

123. The compound of claim 93 wherein A is (C=O).

124. The compound of claim 123 wherein R_4 is methyl.

125. The compound of claim 124 wherein R_2 is H.

126. The compound of claim 125 wherein Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl, butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-methoxyphenyl, 2-chlorophenyl, $-C(CH_3)=CH$, 1-(N-pyridyl)ethyl, or 9-fluoreneylmethyl.

127. The compound of claim 126 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl; and R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

128. The compound of claim 88 selected from the group consiting of:

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea.

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea;

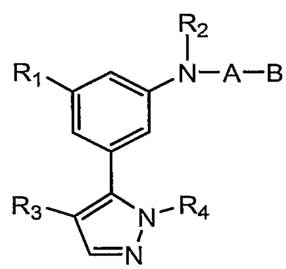
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea

and

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea.

129. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of Formula (I):



(I)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four

substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

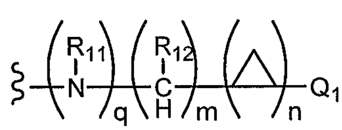
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



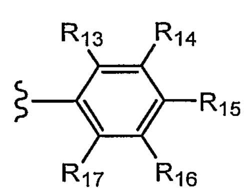
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:

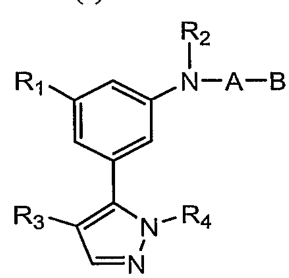


wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

130. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of Formula (I):



(I)

wherein:

i) R_1 is H, halogens, NR_5R_6, OH or OR_7, wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, SO_3R_8, $SO_2NR_8R_9$, COMe,

COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, $CONR_8R_9$, NR_8R_9, $NHCOCH_3$, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, COMe, COEt, CO-lower alkyl, SCF_3, CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen,

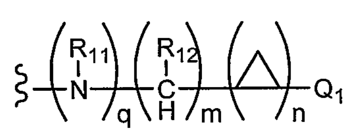
$-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



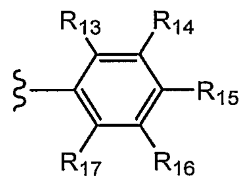
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{2\text{-}6}$ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt; provided that the compound is not any of the following 43 compounds:

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy) phenyl)amino)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-trifluoromethoxy) phenyl)methyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl) phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)-carboxamide;

N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;

N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethylthio)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;

2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-dimethoxyphenylmethyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-trimethoxyphenylmethyl)carboxamide;

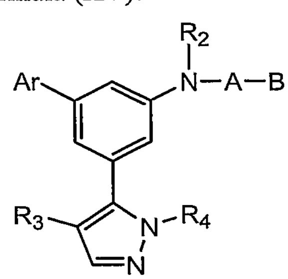
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl) amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenylmethyl)carboxamide

and

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide.

131. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of Formula (**XV**):



(**XV**)

wherein:

i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR_7, OH, NR_8R_9, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl $-C(p)_3$, or $-O-C(p)_3$ where p is halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3, OCF_3, OEt, CCl_3, Me, NO_2, OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10}, COEt, $NHCOCH_3$, or aryl; or

R_8 and R_9 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3, CCl_3, Me, NO_2, OH, OMe, OEt, OCF_3, SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10}, $NHCOCH_3$, COEt, COMe, or halogen;

R_7 is H or C_{1-6} alkyl;

R_{10} is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

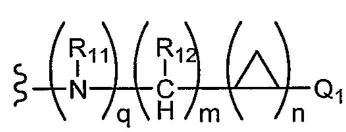
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO_2;

vi) B is L_1 or L_2;

L_1 is:



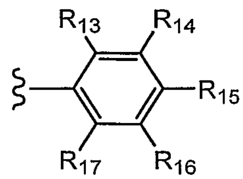
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13}, R_{14}, R_{15}, R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9, $COOR_{10}$, SR_{10}, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_{10}, NR_8R_9, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2, OR_7, halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

132. A pharmaceutical composition comprising a compound of any one of the claims 1, 41-45, 88 and 128.

133. A method for the prophylaxis or treatment of reducing platelet aggregation in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

134. A method for the prophylaxis or treatment of any one of the group of indications consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

135. A method for the prophylaxis or treatment of reducing risk of blood clot formation in an angioplasty or coronary bypass in a surgery patient in need of such prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claims 132.

136. A method for the prophylaxis or treatment of reducing risk of blood clot formation in a patient suffering from atrial fibrillation comprising administering to said patient in need thereof a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

137. A method for the prophylaxis or treatment of asthma in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

138. A method for the prophylaxis or treatment of a symptom of asthma in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

139. A method for the prophylaxis or treatment of agitation or a symptom thereof in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

140. The method of claim 139 wherein said patient is a cognitively intact elderly patient.

141. A method for the prophylaxis or treatment of agitation or a symptom thereof in a patient suffering from dementia, comprising administering to said patient in need thereof a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

142. The method of claim 141 wherein said dementia is due to a degenerative disease of the nervous system.

143. The method of claim 141 wherein said dementia is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease.

144. The method of claim 141 wherein said dementia is due to diseases that affect blood vessels.

145. The method of claim 141 wherein said dementia is due to stroke or multi-infarct dementia.

146. A method for the prophylaxis or treatment of a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, or NOS schizophrenia comprising administering to said patient in need thereof a dopamine D2 receptor antagonist and a according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

147. The method of claim 146 wherein said dopamine D2 receptor antagonist is haloperidol.

148. A method for the prophylaxis or treatment of infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said patient in need thereof a dopamine D2 receptor antagonist and a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

149. The method of claim 148 wherein said dopamine D2 receptor antagonist is haloperidol.

150. A method for the prophylaxis or treatment of schizophrenia in a patient, comprising administering to said patient in need thereof a dopamine D2 receptor antagonist and a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

151. The method of claim 150 wherein said dopamine D2 receptor antagonist is haloperidol.

152. A method for the prophylaxis or treatment of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from said schizophrenia, comprising administering to said patient in need thereof a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

153. The method of any one of claims 147, 149, 151 and 152 wherein said haloperidol and said compound are administered in separate dosage forms.

154. The method of any one of claims 147, 149, 151 and 152 wherein said haloperidol and said compound are administered in a single dosage form.

155. Use of a compound according to any one of claims 1, 41 to 45, 88 and 128 for production of a medicament for use in prophylaxis or treatment of a 5-HT_{2A} related disorder.

156. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing platelet aggregation in a patient in need of said prophylaxis or treatment.

157. The use according to claim 155 wherein the 5-HT_{2A} related disorder is any one of the group of indications consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation in a patient in need of said prophylaxis or treatment.

158. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing risk of blood clot formation in an angioplasty or coronary bypass in a surgery patient in need of such prophylaxis or treatment.

159. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing risk of blood clot formation in a patient suffering from atrial fibrillation.

160. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is asthma.

161. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is agitation.

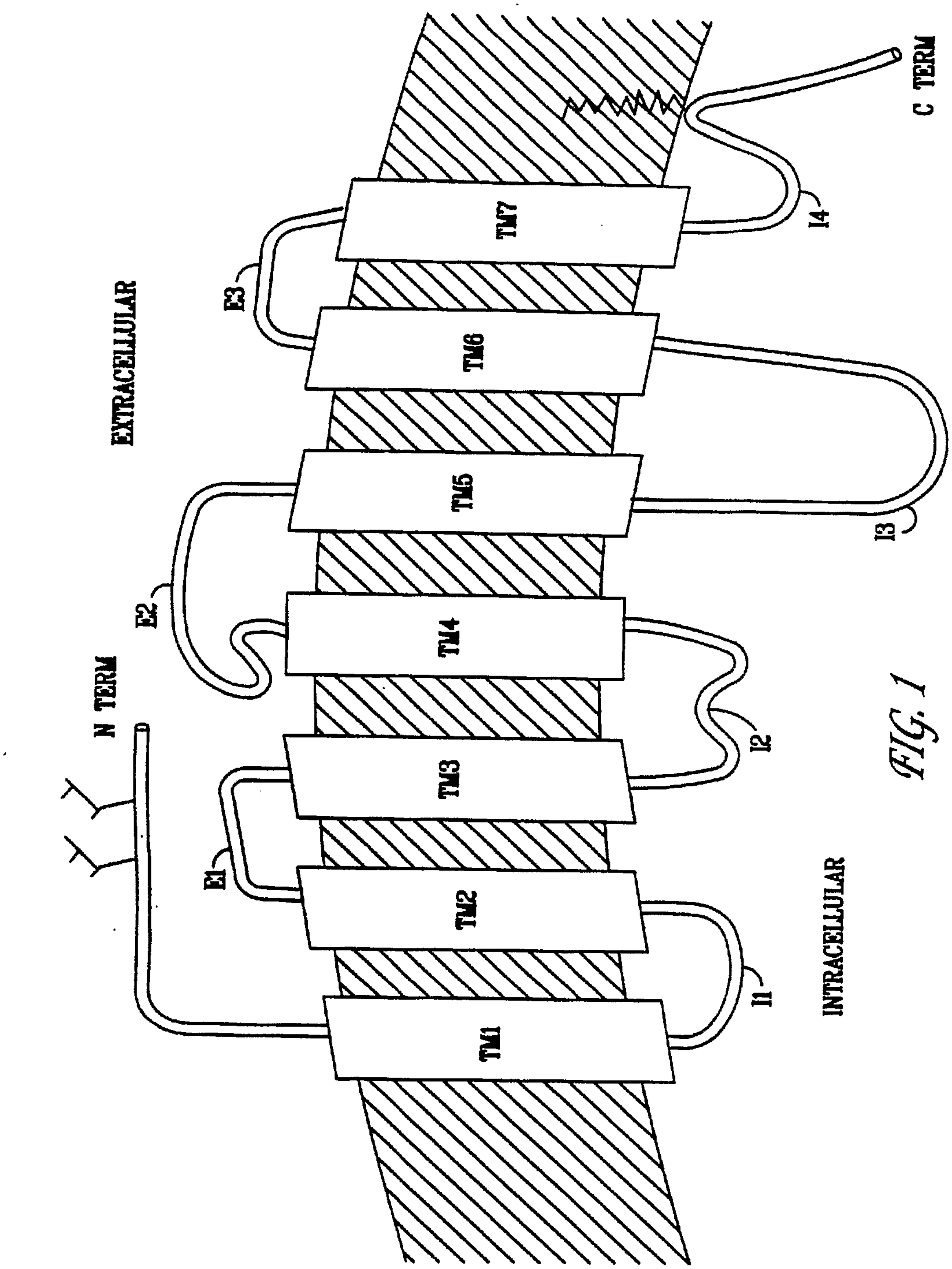
162. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is dementia.

163. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is Alzheimers disease, Lewy Body, Parkinson's disease, or Huntington's disease.

164. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, or NOS schizophrenia.

165. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies.

166. The use according to claim 155 wherein the $5\text{-}HT_{2A}$ related disorder is schizophrenia.


EXTRACELLULAR
INTRACELLULAR
N TERM
C TERM
TM1
TM2
TM3
TM4
TM5
TM6
TM7
E1
E2
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I1
I2
I3
I4

FIG. 1

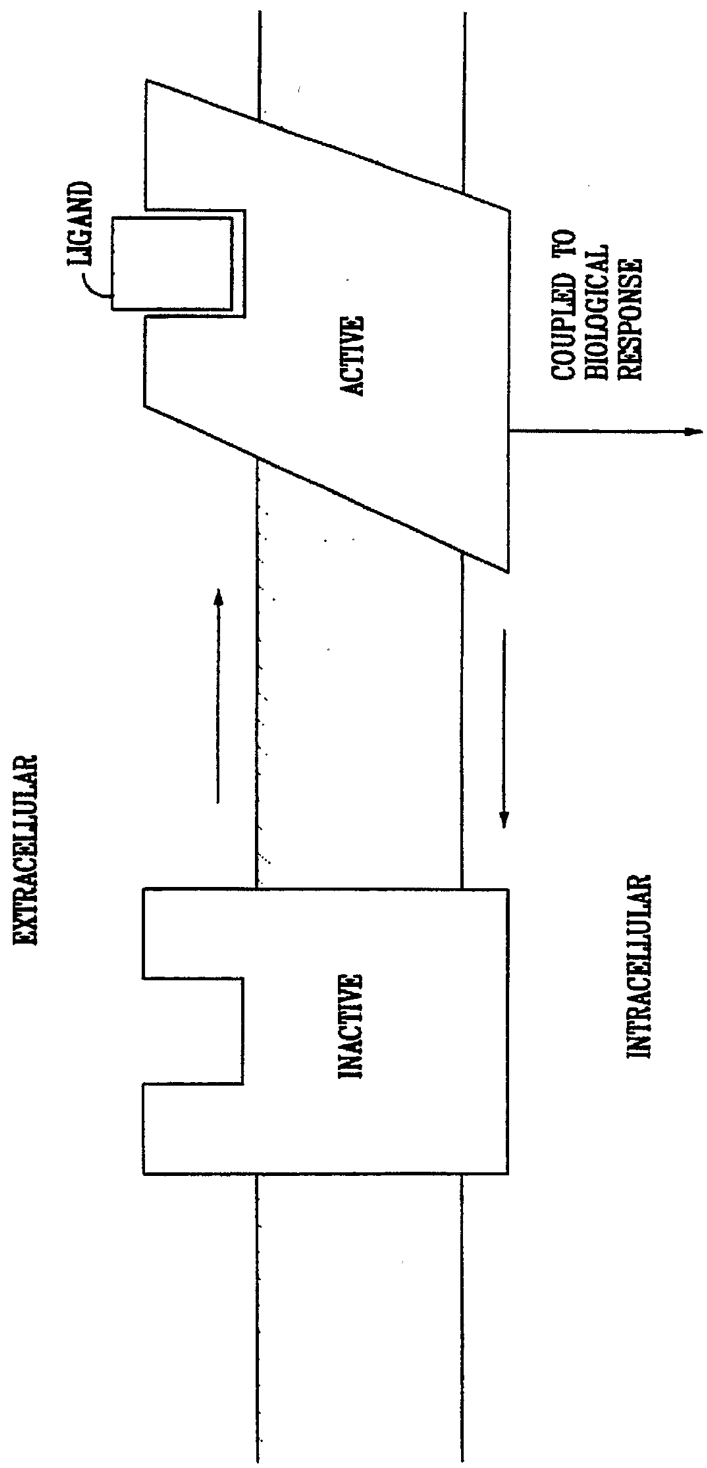
LIGAND
ACTIVE
COUPLED TO BIOLOGICAL RESPONSE
EXTRACELLULAR
INACTIVE
INTRACELLULAR

FIG. 2

FIG. 3A

ATGGATATTCTTTGTGAAGAAAATACTTCTTTGAGCTCAACTACGAACTCCCTAATGCAATTA
AATGATGACAACAGGCTCTACAGTAATGACTTTAACTCCGGAGAAGCTAACACTTCTGATGCA
TTTAACTGGACAGTCGACTCTGAAAATCGAACCAACCTTTCCTGTGAAGGGTGCCTCTCACCG
TCGTGTCTCTCCTTACTTCATCTCCAGGAAAAAAACTGGTCTGCTTTACTGACAGCCGTAGTGA
TTATTCTAACTATTGCTGGAAACATACTCGTCATCATGGCAGTGTCCCTAGAGAAAAAGCTGC
AGAATGCCACCAACTATTTCCTGATGTCACTTGCCATAGCTGATATGCTGCTGGGTTTCCTTGT
CATGCCCGTGTCCATGTTAACCATCCTGTATGGGTACCGGTGGCCTCTGCCGAGCAAGCTTTGT
GCAGTCTGGATTTACCTGGACGTGCTCTTCTCCACGGCCTCCATCATGCACCTCTGCGCCATCT
CGCTGGACCGCTACGTCGCCATCCAGAATCCCATCCACCACAGCCGCTTCAACTCCAGAACTA
AGGCATTTCTGAAAATCATTGCTGTTTGGACCATATCAGTAGGTATATCCATGCCAATACCAG
TCTTTGGGCTACAGGACGATTCGAAGGTCTTTAAGGAGGGGAGTTGCTTACTCGCCGATGATA
ACTTTGTCCTGATCGGCTCTTTTGTGTCATTTTTCATTCCCTTAACCATCATGGTGATCACCTAC
TTTCTAACTATCAAGTCACTCCAGAAAGAAGCTACTTTGTGTGTAAGTGATCTTGGCACACGG
GCCAAATTAGCTTCTTTCAGCTTCCTCCCTCAGAGTTCTTTGTCTTCAGAAAAGCTCTTCCAGC
GGTCGATCCATAGGGAGCCAGGGTCCTACACAGGCAGGAGGACTATGCAGTCCATCAGCAAT
GAGCAAAAGGCATGCAAGGTGCTGGGCATCGTCTTCTTCCTGTTTGTGGTGATGTGGTGCCCT
TTCTTCATCACAAACATCATGGCCGTCATCTGCAAAGAGTCCTGCAATGAGGATGTCATTGGG
GCCCTGCTCAATGTGTTTGTTTGGATCGGTTATCTCTCTTCAGCAGTCAACCCACTAGTCTACA
CACTGTTCAACAAGACCTATAGGTCAGCCTTTTCACGGTATATTCAGTGTCAGTACAAGGAAA
ACAAAAAACCATTGCAGTTAATTTTAGTGAACACAATACCGGCTTTGGCCTACAAGTCTAGCC
AACTTCAAATGGGACAAAAAAAGAATTCAAAGCAAGATGCCAAGACAACAGATAATGACTGC
TCAATGGTTGCTCTAGGAAAGCAGTATTCTGAAGAGGCTTCTAAAGACAATAGCGACGGAGT
GAATGAAAAGGTGAGCTGTGTGTGA

FIG. 3B

MDILCEENTSLSSTTNSLMQLNDDNRLYSNDFNSGEANTSDAFNWTVDSENRTNLSCEGCLSPSCL
SLLHLQEKNWSALLTAVVIILTIAGNILVIMAVSLEKKLQNATNYFLMSLAIADMLLGFLVMPVSM
LTILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISLDRYVAIQNPIHHSRFNSRTKAFLKIIAVW
TISVGISMPIPVFGLQDDSKVFKEGSCLLADDNFVLIGSFVSFFIPLTIMVITYFLTIKSLQKEATLCVS
DLGTRAKLASFSFLPQSSLSSEKLFQRSIHREPGSYTGRRTMQSISNEQKACKVLGIVFFLFVVMWC
PFFITNIMAVICKESCNEDVIGALLNVFVWIGYLSSAVNPLVYTLFNKTYRSAFSRYIQCQYKENKK
PLQLILVNTIPALAYKSSQLQMGQKKNSKQDAKTTDNDCSMVALGKQYSEEASKDNSDGVNEKV
SCV

FIG. 4B

MVNLRNAVHSFLVHLIGLLVWQCDISVSPVAAIVTDIFNTSDGGRFKFPDGVQNWPALSIVIIIIMTIGGN
ILVIMAVSMEKKLHNATNYFLMSLAIADMLVGLLVMPLSLLAILYDYVWPLPRYLCPVWISLDVLFSTASI
MHLCAISLDRYVAIRNPIEHSRFNSRTKAIMKIAIVWAISIGVSVPIPVIGLRDEEKVFVNNTTCVLNDPN
FVLIGSFVAFFIPLTIMVITYCLTIYVLRRQALMLLHGHTEEPPGLSLDFLKCCKRNTAEEENSANPNQDQ
NARRRKKKERRPRGTMQAINNERKASKVLGIVFFVFLIMWCPFFITNILSVLCEKSCNQKLMEKLLNVFVW
IGYVCSGINPLVYTLFNKIYRRAFSNYLRCNYKVEKKPPVRQIPRVAATALSGRELNVNIYRHTNEPVIEK
ASDNEPGIEMQVENLELPVNPSSVVSERISSV

FIG. 4A

ATGGTGAACCTGAGGAATGCGGTGCATTCATTCCTTGTGCACCTAATTGGCCTATTGGTTTGGC
AATGTGATATTTCTGTGAGCCCAGTAGCAGCTATAGTAACTGACATTTTCAATACCTCCGATG
GTGGACGCTTCAAATTCCCAGACGGGGTACAAAACTGGCCAGCACTTTCAATCGTCATCATAA
TAATCATGACAATAGGTGGCAACATCCTTGTGATCATGGCAGTAAGCATGGAAAAGAAACTG
CACAATGCCACCAATTACTTCTTAATGTCCCTAGCCATTGCTGATATGCTAGTGGGACTACTTG
TCATGCCCCTGTCTCTCCTGGCAATCCTTTATGATTATGTCTGGCCACTACCTAGATATTTGTG
CCCCGTCTGGATTTCTTTAGATGTTTTATTTTCAACAGCGTCCATCATGCACCTCTGCGCTATAT
CGCTGGATCGGTATGTAGCAATACGTAATCCTATTGAGCATAGCCGTTTCAATTCGCGGACTA
AGGCCATCATGAAGATTGCTATTGTTTGGGCAATTTCTATAGGTGTATCAGTTCCTATCCCTGT
GATTGGACTGAGGGACGAAGAAAAGGTGTTCGTGAACAACACGACGTGCGTGCTCAACGACC
CAAATTTCGTTCTTATTGGGTCCTTCGTAGCTTTCTTCATACCGCTGACGATTATGGTGATTAC
GTATTGCCTGACCATCTACGTTCTGCGCCGACAAGCTTTGATGTTACTGCACGGCCACACCGA
GGAACCGCCTGGACTAAGTCTGGATTTCCTGAAGTGCTGCAAGAGGAATACGGCCGAGGAAG
AGAACTCTGCAAACCCTAACCAAGACCAGAACGCACGCCGAAGAAAGAAGAAGGAGAGACG
TCCTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTTCGAAAGTCCTTGGGATTG
TTTTCTTTGTGTTTCTGATCATGTGGTGCCCATTTTTCATTACCAATATTCTGTCTGTTCTTTGTG
AGAAGTCCTGTAACCAAAAGCTCATGGAAAAGCTTCTGAATGTTGTTTGTTTGGATTGGCTAG
TTTGTTCAGGAATCAATCCTCTGGTGTATACTCTGTTCAACAAAATTTACCGAAGGGCATTCTC
CAACTATTTGCGTTGCAATTATAAGGTAGAGAAAAAGCCTCCTGTCAGGCAGATTCCAAGAGT
TGCCGCCACTGCTTTGTCTGGGAGGGAGCTTAATGTTAACATTTATCGGCATACCAATGAACC
GGTGATCGAGAAAGCCAGTGACAATGAGCCCGGTATAGAGATGCAAGTTGAGAATTTAGAGT
TACCAGTAAATCCCTCCAGTGTGGTTAGCGAAAGGATTAGCAGTGTGTGA

FIG. 5A

ATGGTGAACCTGAGGAATGCGGTGCATTCATTCCTTGTGCACCTAATTGGCCTATTGGTTTGGCAAT
GTGATATTTCTGTGAGCCCAGTAGCAGCTATAGTAACTGACATTTTCAATACCTCCGATGGTGGACG
CTTCAAATTCCCAGACGGGGTACAAAACTGGCCAGCACTTTCAATCGTCATCATAATAATCATGAC
AATAGGTCGCAACATCCTTGTGATCATGGCAGTAAGCATGGAAAAGAAACTGCACAATGCCACCA
ATTACTTCTTAATGTCCCTAGCCATTGCTGATATGCTAGTGGGACTACTTGTCATGCCCCTGTCTCTC
CTGGCAATCCTTTATGATTATGTCTGGCCATCAACTAGATATTTGTGCCCGTCTGGATTTCTTTAGA
TGTTTTATTTTCAACAGCGTCCATCATGCACCTCTGCGCTATATCGCTGGATCGGTATGTAGCAATA
CGTAATTCTATTGAGCATAGCCGTTTCAATTCGCGGACTAAGGCCATCATGAAGATTGCTATTGTTT
GGGCAATTTCTATAGGTGTATCAGTTCCTATCCCTGTGATTGGACTGAGGGACGAAGAAAAGGTGT
TCGTGAACAACACGACGTGCGTGCTCAACGACCCAAATTTGCTTCTTATTGGGTCCTTCGTAGCTTT
CTTCATACCGCTGACGATTATGGTGATTACGTATTGCCTGACCATCTACGTTCTGCGCCGACAAGCT
TTGATGTTACTGCACGGCCACACCGAGGAACCGCCTGGACTAAGTCTGTATTTCCTGAACTGCTGC
AAGAGGAATACGGCCGAGGAAGAGAACTCTGCAAACCCTAACCAAGACCAGAACGCACGCCGAA
GAAAGAAGAAGGAGAGACGTCCTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTAA
GAAAGTCCTTGGGATTGTTTTCTTTGTGTTTCTGATCATGTGGTGCCCATTTTTCATTACCAATATTC
TGTCTGTTCTTTGTGAGAAGTCCTGTAACCAAAAGCTCATGGAAAAGCTCTGAATGTGTTTGTTTG
GATTGGCTATGTTTGTTCAGGATTCAATCCTCTGGTGTATACTCTGTTCAACAAAATTTACCGAAGG
GCATTCTCCAACTATTTGCGTTGCAATTATAAGGTAGAGAAAAAGCCCTCCTGTCAGGCAGATTCCA
AGAGTTGCCGCCACTGCTTTGTCTGGGAGGGAGCTTATTGTTAACATTTATCGGCATACCAATGAA
CCGGTGATCGAGAAAGCCAGTGACAATGAGCCCGGTATAGAGATGCAAGTTGAGAATTTAGAGTT
ACCAGTAAATCCCTCCAGTGTGGTTAGCGAAAGGATTAGCAGTGTGTGA

FIG. 5B

MVNLRNAVHSFLVHLIGLLVWQCDISVSPVAAIVTDIFNTSDGGRFKFPDGVQNWPALSIVIIIIMTI
GGNILVIMAVSMEKKLHNATNYFLMSLAIADMLVGLLVMPLSLLAILYDYVWPLPRYLCPVWISL
DVLFSTASIMHLCAISLDRYVAIRNPIEHSRFNSRTKAIMKIAIVWAISIGVSVPIPVIGLRDEEKVFV
NNTTCVLNDPNFVLIGSFVAFFIPLTIMVITYCLTIYVLRRQALMLLHGHTEEPPGLSDFLKCCKRN
TAEEENSANPNQDQNARRRKKKERRPRGTMQAINNERKAKKVLGIVFFVFLIMWCPFFITNILSVL
CEKSCNQKLMEKLLNVFVWIGYVCSGINPLVYTLFNKIYRRAFSNYLRCNYKVEKKPPVRQIPRV
AATALSGRENLNVNIYRHTNEPVIEKASDNEPGIEMQVENLELPVNPSSVVSERISSV

FIG. 6B

MDILCEENTSLSSTTNSLMQLNDDNRLYSNDFNSGEANTSDAFNWTVDSENRTNLSCEGCLSPSCL
SLLHLQEKNWSALLTAVVIILLTIAGNILVIMAVSLEKKLQNATNYFLMSLAIADMLLGFLVMPVSM
LTILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISLDRYVAIQNPIHHSRFNSRTKAFLKIIAVW
TISVGISMPIPVFGLQDDSKVFKEGSCLLADDNFVLIGSFVSFFIPLTIMVITYFLTIKVLRRQALMLL
HGHTEEPPGLSLDFLKCCKRNTAEEENSANPNQDQNARRRKKKERRPRGTMQAINNERKAS
KVLGIVFFLFVVMWCPFFITNIMAVICKESCNEDVIGALLNVFVWIGYLSSAVNPLVYTLFNKIYR
RAFSNYLRCNYKVEKKPPVRQIPRVAATALSGRELNVNIYRHTNEPVIEKASDNEPGIEMQVE
NLELPVNPSSVVSERISSV

FIG. 6C

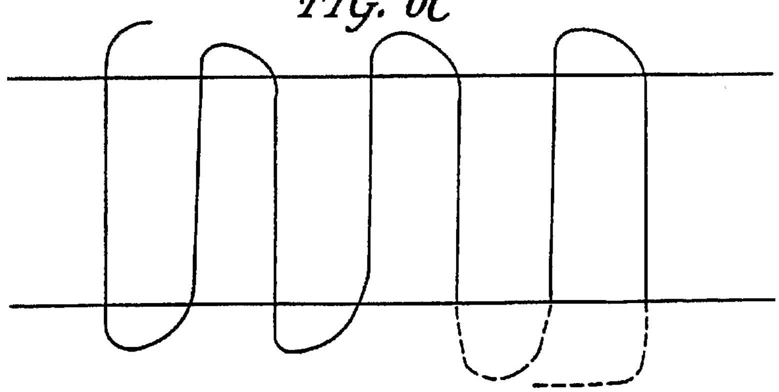

FIG. 6A

ATGGATATTCTTTGTGAAGAAAATACTTCTTTGAGCTCAACTACGAACTCCCTAATGCAATTA
AATGATGACAACAGGCTCTACAGTAATGACTTTAACTCCGGAGAAGCTAACACTTCTGATGCA
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TCGTGTCTCTCCTTACTTCATCTCAGGAAAAAAACTGGTCTGCTTTACTGACAGCCGTAGTGA
TTATTCTAACTATTGCTGGAAACATACTCGTCATCATGGCAGTGTCCCTAGAGAAAAAGCTGC
AGAATGCCACCAACTATTTCCTGATGTCACTTGCCATAGCTGATATGCTGCTGGGTTTCCTTGT
CATGCCCGTGTCCATGTTAACCATCCTGTATGGGTACCGGTGGCCTCTGCCGAGCAAGCTTTGT
GCAGTCTGGATTTACCTGGACGTGCTCTTCTCCACGGCCTCCATCATGCACCTCTGCGCCATCT
CGCTGGACCGCTACGTCGCCATCCAGAATCCCATCCACCACAGCCGCTTCAACTCCAGAACTA
AGGCATTTCTGAAAATCATTGCTGTTTGGACCATATCAGTAGGTATATCCATGCCAATACCAG
TCTTTGGGCTACAGGACGATTCGAAGGTCTTTAAGGAGGGGAGTTGCTTACTCGCCGATGATA
ACTTTGTCTGATCGGCTCTTTTGTGTCATTTTTCATTCCCTTAACCATCATGGTGATCACCTAC
TTTCTAACTATCAAGGTTCTGCGCCCGACAAGCTTTGATGTTACTGCACGGCCACACCGAG
GAACCGCCTGGACTAAGTCTGGATTTCCTGAAGTGCTGCAAGAGGAATACGGCCGAGGA
AGAGAACTCTGCAAACCCTAACCAAGACCAGAACGCACGCCGAAGAAAGAAGAAGGAG
AGACGTCCTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTTCGAAGGTACT
GGGCATCGTCTTCTTCCTGTTTGTGGTGATGTGGTGCCCTTTCTTCATCACAAACATCATGGCC
GTCATCTGCAAAGAGTCCTGCAATGAGGATGTCATTGGGGCCCTGCTCAATGTGTTTGTTTGG
ATCGGTTATCTCTCTTCAGCAGTCAACCCACTAGTCTATACTCTGTTCAACAAAATTTACCGA
AGGGCATTCTCCAACTATTTGCGTTGCAATTATAAGGTAGAGAAAAAGCCTCCTGTCAG
GCAGATTCCAAGAGTTGCCGCCACTGCTTTGTCTGGGAGGGAGCTTAATGTTAACATTT
ATCGGCATACCAATGAACCGGTGATCGAGAAAGCCAGTGACAATGAGCCCGGTATAGAG
ATGCAAGTTGAGAATTTAGAGTTACAGTAAATCCCTCCAGTGTGGTTAGCGAAAGGAT
TAGCAGTGTGTGA

FIG. 7A

ATGGATATTCTTTGTGAAGAAAATACTTCTTTGAGCTCAACTACGAACTCCCTAATGCAATTA
AATGATGACAACAGGCTCTACAGTAATGACTTTAACTCCGGAGAAGCTAACACTTCTGATGCA
TTTAACTGGACAGTCGACTCTGAAAATCGAACCAACCTTTCCTGTGAAGGGTGCCTCTCACCG
TCGTGTCTCTCCTTACTTCATCTCCAGGAAAAAAACTGGTCTGCTTTACTGACAGCCGTAGTGA
TTATTCTAACTATTGCTGGAAACATACTCGTCATCATGGCAGTGTCCCTAGAGAAAAAGCTGC
AGAATGCCACCAACTATTTCCTGATGTCACTTGCCATAGCTGATATGCTGCTGGGTTTCCTTGT
CATGCCCGTGTCCATGTTAACCATCCTGTATGGGTACCGGTGGCCTCTGCCGAGCAAGCTTTGT
GCAGTCTGGATTTACCTGGACGTGCTCTTCTCCACGGCCTCCATCATGCACCTCTGCGCCATCT
CGCTGGACCGCTACGTCGCCATCCAGAATCCCATCCACCACAGCCGCTTCAACTCCAGAACTA
AGGCATTTCTGAAAATCATTGCTGTTTGGACCATATCAGTAGGTATATCCATGCCAATACCAG
TCTTTGGGCTACAGGACGATTCGAAGGTCTTTAAGGAGGGGAGTTGCTTACTCGCCGATGATA
ACTTTGTCCTGATCGGCTCTTTTGTGTCATTTTTCATTCCCCTGACGATTATGGTGATTACGT
ATTGCCTGACCATCTACGTTCTGCGCCGACAAGCTTTGATGTTACTGCACGGCCACACC
GAGGAACCGCCTGGACTAAGTCTGGATTTCCTGAAGTGCTGCAAGAGGAATACGGCCGA
GGAAGAGAACTCTGCAAACCCTAACCAAGACCAGAACGCACGCCGAAGAAAGAAGAAG
GAGAGACGTCCTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTAAGAAAGT
CCTTGGGATTGTTTTCTTTGTGTTTCTGATCATGTGGTGCCCTTTCTTCATCACAAACATCA
TGGCCGTCATCTGCAAAGAGTCCTGCAATGAGGATGTCATTGGGGCCCTGCTCAATGTGTTTG
TTTGGATCGGTTATCTCTCTTCAGCAGTCAACCCACTAGTCTATACTCTGTTCAACAAAATTT
ACCGAAGGGCATTCTCCAACTATTTGCGTTGCAATTATAAGGTAGAGAAAAAGCCTCCT
GTCAGGCAGATTCCAAGAGTTGCCGCCACTGCTTTGTCTGGGAGGGAGCTTAATGTTAA
CATTTATCGGCATACCAATGAACCGGTGATCGAGAAAGCCAGTGACAATGAGCCCGGTA
TAGAGATGCAAGTTGAGAATTTAGAGTTACCAGTAAATCCCTCCAGTGTGGTTAGCGAA
AGGATTAGCAGTGTGTGA

FIG. 7B

MDILCEENTSLSSTTNSLMQLNDDNRLYSNDFNSGEANTSDAFNWTVDSENRTNLSCEGCLSPSCL
SLLHLQEKNWSALLTAVVIILTIAGNILVIMAVSLEKKLQNATNYFLMSLAIADMLLGFLVMPVSM
LTILYGYRWPLPSKLCAVWIYLDVLFSTASIMHLCAISLDRYVAIQNPIHHRSFNSRTKAFLKIIAVW
TISVGISMPIPVFGLQDDSKVFKEGSCLLADDNFVLIGSFVSFFIPLTIMVTTYCLTIYVLRRQALML
LHGHTEEPPGLSLDFLKCCKRNTAEEENSANPNQDQNARRRKKKERRPRGTMQAINNERKA
KKVLGIVFFVFLIMWCPFFITNIMAVICKESCNEDVIGALLNVFVWIGYLSSAVNPLVYTLFNKIY
RRAFSNYLRCNYKVEKKPPVRQIPRVAATALSGRELNVNIYRHTNEPVIEKASDNEPGIEMQV
ENLELPVNPSSVVSERISSV

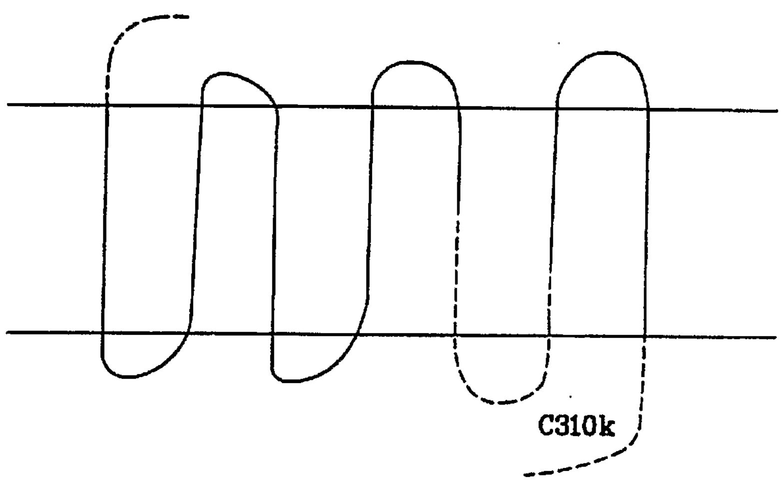
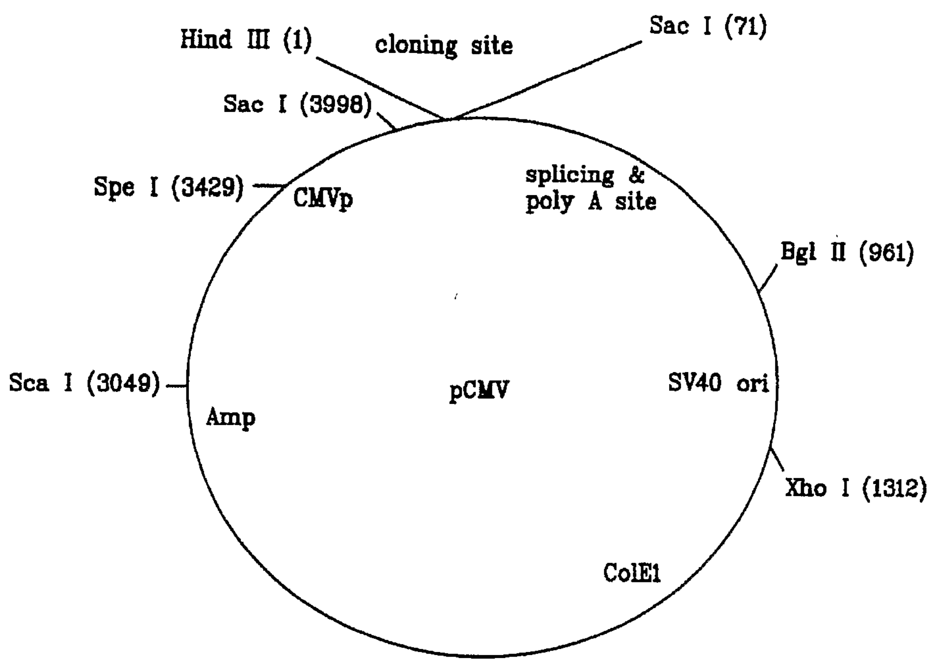


FIG. 7C



*Xho I (1312) to Sca I (3049) is identical to pRc/RSV Xho I (3045) to 4782.
*Sca I (3049) to 4070 is identical to pCDM7 Amp ScaI (2524) to 3545.
*multiple cloning site includes Hind III to Sac I of pBluescript II.
*110 to 1312 is identical to pCMD7 Amp 76 to 1278.
*Sac I and Spe I in MCS are not unique.

FIG. 8

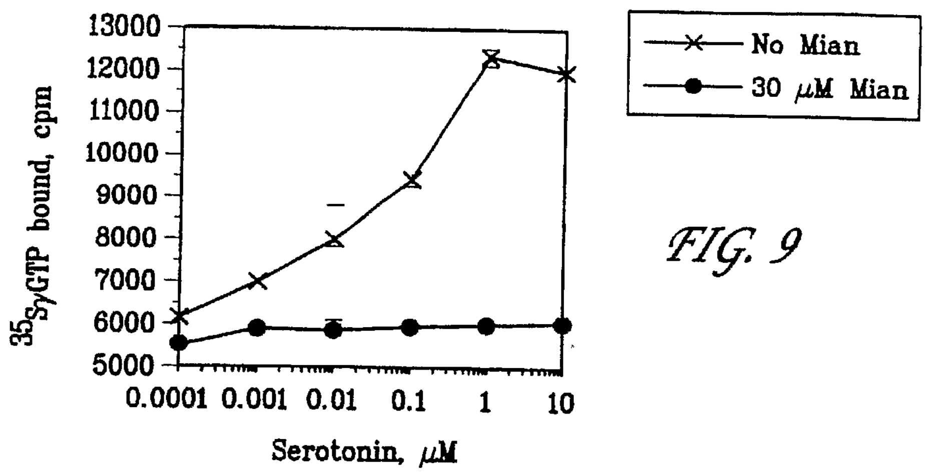

13000
12000
11000
10000
9000
8000
7000
6000
5000
^{35}SγGTP bound, cpm
0.0001 0.001 0.01 0.1 1 10
Serotonin, μM
No Mian
30 μM Mian

FIG. 9

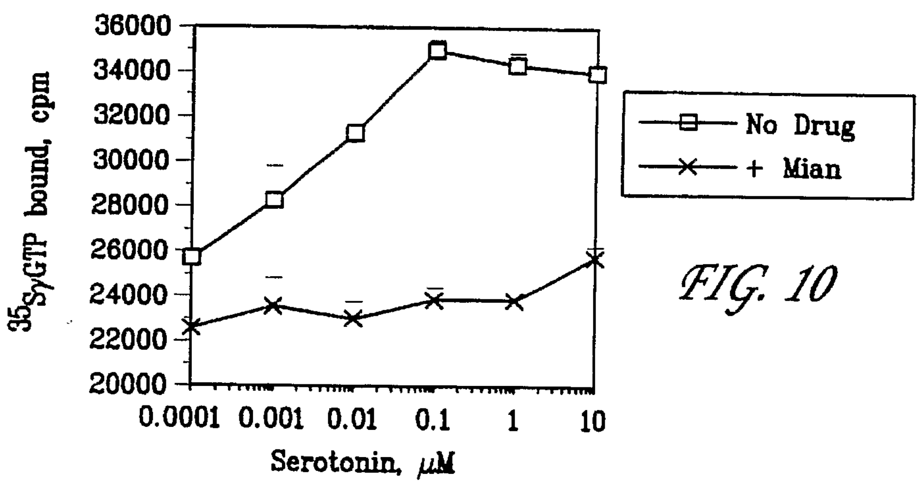

36000
34000
32000
30000
28000
26000
24000
22000
20000
^{35}SγGTP bound, cpm
0.0001 0.001 0.01 0.1 1 10
Serotonin, μM
No Drug
+ Mian

FIG. 10

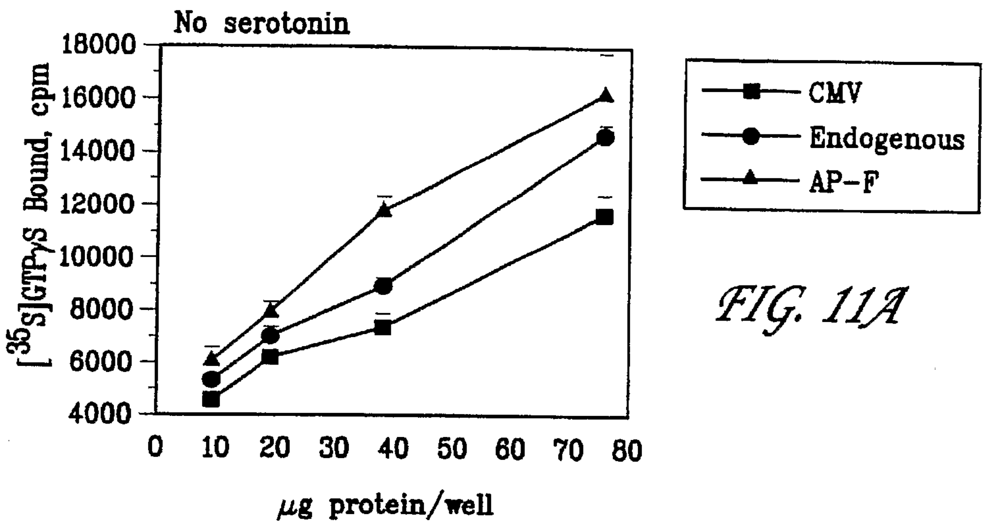


FIG. 11A

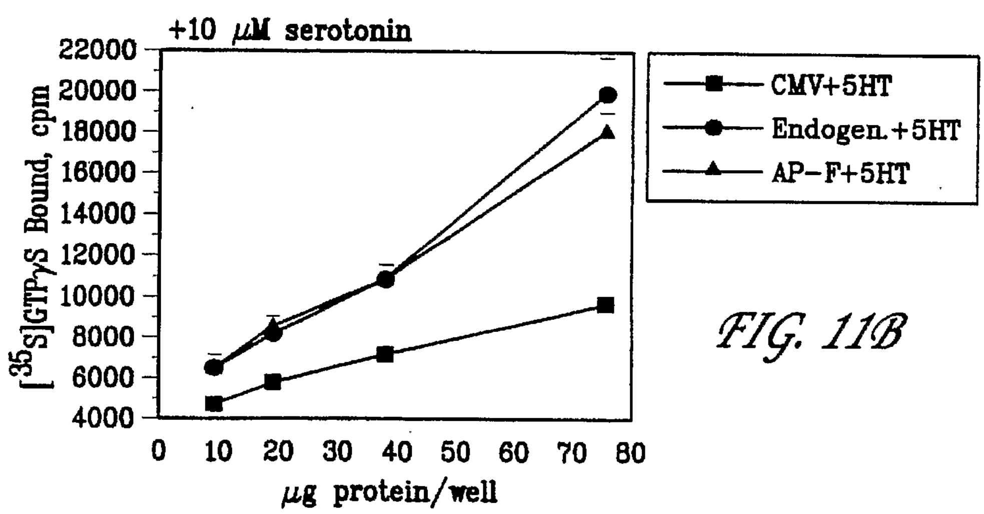


FIG. 11B

FIG. 12

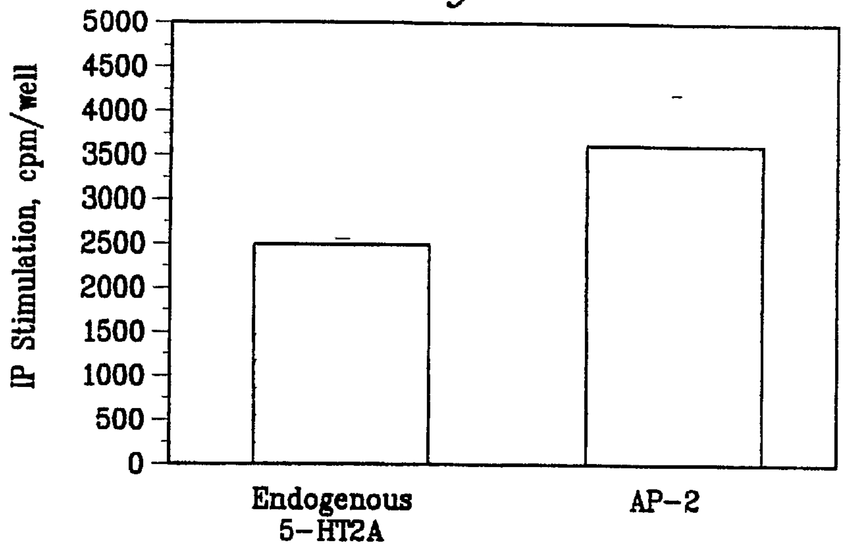
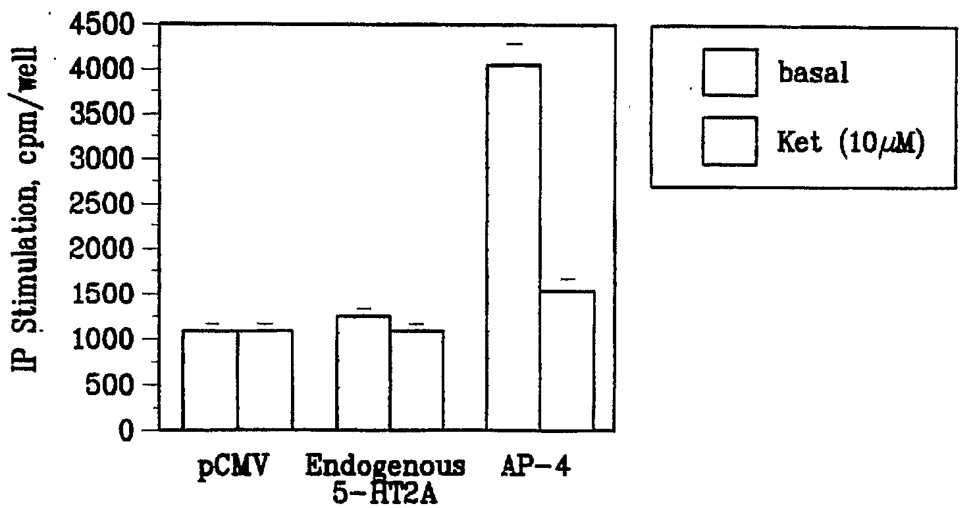

IP Stimulation, cpm/well
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Endogenous 5-HT2A
AP-2

FIG. 13


IP Stimulation, cpm/well
4500
4000
3500
3000
2500
2000
1500
1000
500
0
pCMV
Endogenous 5-HT2A
AP-4
basal
Ket (10μM)

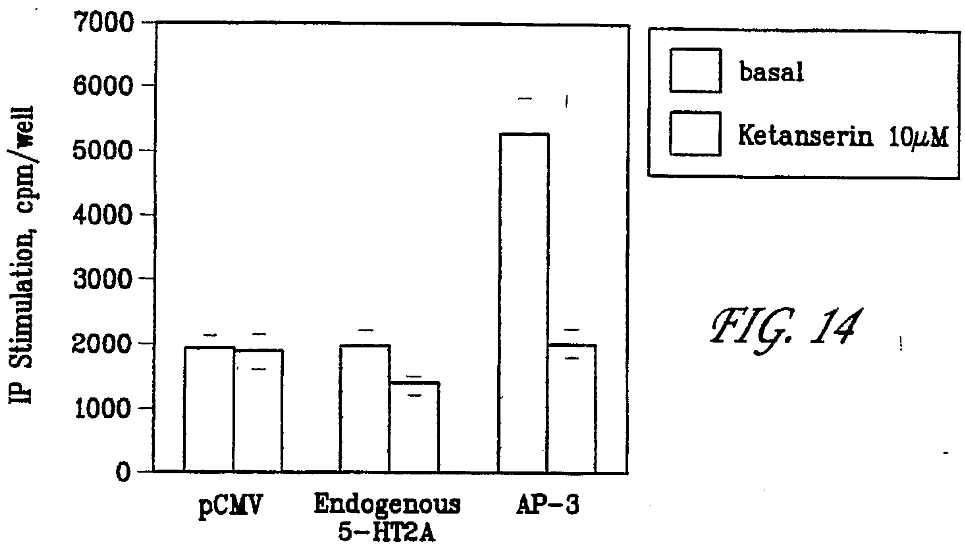
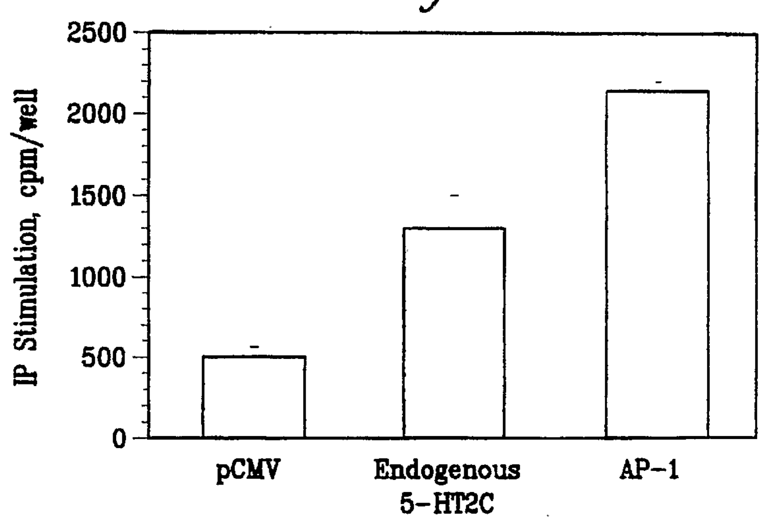

7000
6000
5000
4000
3000
2000
1000
0
IP Stimulation, cpm/well
basal
Ketanserin 10μM
pCMV
Endogenous
5-HT2A
AP-3

FIG. 14

FIG. 15


2500
2000
1500
1000
500
0
IP Stimulation, cpm/well
pCMV
Endogenous
5-HT2C
AP-1

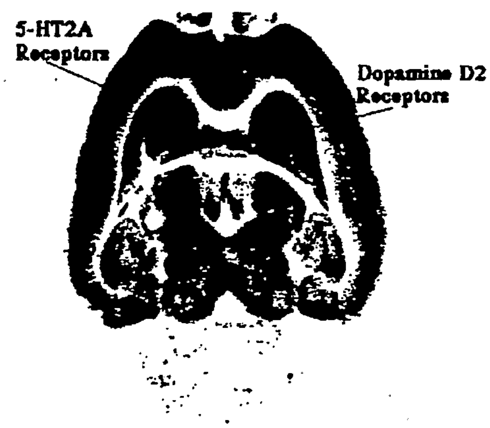
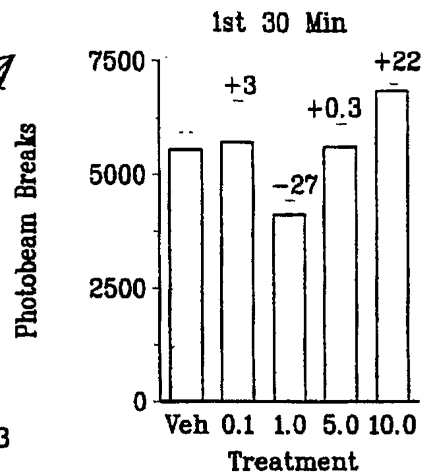


FIG. 16A

FIG. 16B

FIG. 16C

FIG. 17A



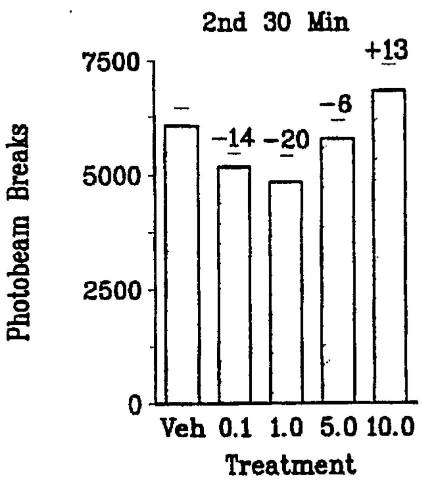


FIG. 17B

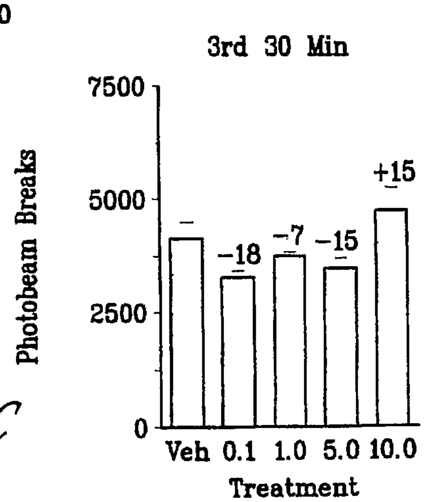


FIG. 17C

9.WO3
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<110> Arena Pharmaceuticals, Inc.
Teegarden, Bradley
Drouet, Keith
Jayakumar, Honnappa
Thomsen, William J.
Maffuid, Paul
Elwell, Katie
Foster, Richard J.
Glen, Robert C.
Lawless, Michael S.
Liu, Qian
Smith, Julian R.
Feichtinger, Konrad

<120> SMALL MOLECULE MODULATORS OF THE 5-HT2A SEROTONIN RECEPTOR USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO

<130> 9.WO3

<160> 31

<170> PatentIn version 3.2

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<220>
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9.WO3

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<220>
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<210> 9
<211> 38
<212> DNA
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9.WO3

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<212> DNA
<213> Artificial

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<210> 13
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<213> Artificial

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<220>
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<211> 43
<212> DNA
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<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

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gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaagggtgc 180

ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactggtc tgctttactg 240

acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc 300

ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat 360

atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccatcctgta tgggtaccgg 420

tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg 480

gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc 540

atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg 600

accatatcag taggtatatc catgccaata ccagtctttg ggctacagga cgattcgaag 660

gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt 720

gtgtcatttt tcattccctt aaccatcatg gtgatcacct actttctaac tatcaagtca 780

ctccagaaag aagctacttt gtgtgtaagt gatcttggca cacgggccaa attagcttct 840

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agggagccag ggtcctacac aggcaggagg actatgcagt ccatcagcaa tgagcaaaag 960

gcatgcaagg tgctgggcat cgtcttcttc ctgtttgtgg tgatgtggtg ccctttcttc 1020

atcacaaaca tcatggccgt catctgcaaa gagtcctgca atgaggatgt cattggggcc 1080

ctgctcaatg tgtttgtttg gatcggttat ctctcttcag cagtcaaccc actagtctac 1140

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aatgactgct caatggttgc tctaggaaag cagtattctg aagaggcttc taaagacaat 1380

agcgacggag tgaatgaaaa ggtgagctgt gtgtga 1416

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<213> Homo sapiens

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20 25 30

Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
35 40 45

Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
50 55 60

Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
65 70 75 80

Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
85 90 95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
100 105 110

Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
115 120 125

Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
130 135 140

Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
145 150 155 160

Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
165 170 175

Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
180 185 190

Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
195 200 205

Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
210 215 220

Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
225 230 235 240

Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Phe Leu
245 250 255

Thr Ile Lys Ser Leu Gln Lys Glu Ala Thr Leu Cys Val Ser Asp Leu
260 265 270

9.WO3

Gly Thr Arg Ala Lys Leu Ala Ser Phe Ser Phe Leu Pro Gln Ser Ser
275 280 285

Leu Ser Ser Glu Lys Leu Phe Gln Arg Ser Ile His Arg Glu Pro Gly
290 295 300

Ser Tyr Thr Gly Arg Arg Thr Met Gln Ser Ile Ser Asn Glu Gln Lys
305 310 315 320

Ala Cys Lys Val Leu Gly Ile Val Phe Phe Leu Phe Val Val Met Trp
325 330 335

Cys Pro Phe Phe Ile Thr Asn Ile Met Ala Val Ile Cys Lys Glu Ser
340 345 350

Cys Asn Glu Asp Val Ile Gly Ala Leu Leu Asn Val Phe Val Trp Ile
355 360 365

Gly Tyr Leu Ser Ser Ala Val Asn Pro Leu Val Tyr Thr Leu Phe Asn
370 375 380

Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr Ile Gln Cys Gln Tyr Lys
385 390 395 400

Glu Asn Lys Lys Pro Leu Gln Leu Ile Leu Val Asn Thr Ile Pro Ala
405 410 415

Leu Ala Tyr Lys Ser Ser Gln Leu Gln Met Gly Gln Lys Lys Asn Ser
420 425 430

Lys Gln Asp Ala Lys Thr Thr Asp Asn Asp Cys Ser Met Val Ala Leu
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Asn Glu Lys Val Ser Cys Val
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aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1200

gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1260

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<210> 25
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<212> PRT
<213> Homo sapiens

<400> 25

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Gly Leu Leu Val Trp Gln Cys Asp Ile Ser Val Ser Pro Val Ala Ala
20 25 30

Ile Val Thr Asp Ile Phe Asn Thr Ser Asp Gly Gly Arg Phe Lys Phe
35 40 45

Pro Asp Gly Val Gln Asn Trp Pro Ala Leu Ser Ile Val Ile Ile Ile
50 55 60

Ile Met Thr Ile Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Met
65 70 75 80

Glu Lys Lys Leu His Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala
85 90 95

9.WO3

Ile Ala Asp Met Leu Val Gly Leu Leu Val Met Pro Leu Ser Leu Leu
100 105 110

Ala Ile Leu Tyr Asp Tyr Val Trp Pro Leu Pro Arg Tyr Leu Cys Pro
115 120 125

Val Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met His
130 135 140

Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala Ile Arg Asn Pro Ile
145 150 155 160

Glu His Ser Arg Phe Asn Ser Arg Thr Lys Ala Ile Met Lys Ile Ala
165 170 175

Ile Val Trp Ala Ile Ser Ile Gly Val Ser Val Pro Ile Pro Val Ile
180 185 190

Gly Leu Arg Asp Glu Glu Lys Val Phe Val Asn Asn Thr Thr Cys Val
195 200 205

Leu Asn Asp Pro Asn Phe Val Leu Ile Gly Ser Phe Val Ala Phe Phe
210 215 220

Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Cys Leu Thr Ile Tyr Val
225 230 235 240

Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His Thr Glu Glu Pro
245 250 255

Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys Arg Asn Thr Ala
260 265 270

Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln Asn Ala Arg Arg
275 280 285

Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met Gln Ala Ile Asn
290 295 300

Asn Glu Arg Lys Ala Ser Lys Val Leu Gly Ile Val Phe Phe Val Phe
305 310 315 320

Leu Ile Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Leu Ser Val Leu
325 330 335

Cys Glu Lys Ser Cys Asn Gln Lys Leu Met Glu Lys Leu Leu Asn Val
340 345 350

Phe Val Trp Ile Gly Tyr Val Cys Ser Gly Ile Asn Pro Leu Val Tyr
355 360 365

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Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser Asn Tyr Leu Arg
    370                 375                 380

Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg Gln Ile Pro Arg
385                 390                 395                 400

Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn Val Asn Ile Tyr
                405                 410                 415

Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser Asp Asn Glu Pro
            420                 425                 430

Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro Val Asn Pro Ser
        435                 440                 445

Ser Val Val Ser Glu Arg Ile Ser Ser Val
    450                 455

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tccgatggtg gacgcttcaa attcccagac ggggtacaaa actggccagc actttcaatc     180

gtcatcataa taatcatgac aataggtggc aacatccttg tgatcatggc agtaagcatg     240

gaaaagaaac tgcacaatgc caccaattac ttcttaatgt ccctagccat tgctgatatg     300

ctagtgggac tacttgtcat gcccctgtct ctcctggcaa tcctttatga ttatgtctgg     360

ccactaccta gatatttgtg ccccgtctgg atttctttag atgttttatt ttcaacagcg     420

tccatcatgc acctctgcgc tatatcgctg gatcggtatg tagcaatacg taatcctatt     480

gagcatagcc gtttcaattc gcggactaag gccatcatga agattgctat tgtttgggca     540

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ttcgtgaaca acacgacgtg cgtgctcaac gacccaaatt tcgttcttat tgggtccttc     660

gtagctttct tcataccgct gacgattatg gtgattacgt attgcctgac catctacgtt     720

ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt     780

ctggatttcc tgaagtgctg caagaggaat acggccgagg aagagaactc tgcaaacccct     840

aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg     900

caggctatca acaatgaaag aaaagctaag aaagtccttg ggattgtttt ctttgtgttt     960

ctgatcatgt ggtgcccatt tttcattacc aatattctgt ctgttctttg tgagaagtcc    1020
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9.WO3

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aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1200

gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1260

gaaccggtga tcgagaaagc cagtgacaat gagcccggta tagagatgca agttgagaat 1320

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20 25 30

Ile Val Thr Asp Ile Phe Asn Thr Ser Asp Gly Gly Arg Phe Lys Phe
35 40 45

Pro Asp Gly Val Gln Asn Trp Pro Ala Leu Ser Ile Val Ile Ile Ile
50 55 60

Ile Met Thr Ile Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Met
65 70 75 80

Glu Lys Lys Leu His Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala
85 90 95

Ile Ala Asp Met Leu Val Gly Leu Leu Val Met Pro Leu Ser Leu Leu
100 105 110

Ala Ile Leu Tyr Asp Tyr Val Trp Pro Leu Pro Arg Tyr Leu Cys Pro
115 120 125

Val Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met His
130 135 140

Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala Ile Arg Asn Pro Ile
145 150 155 160

Glu His Ser Arg Phe Asn Ser Arg Thr Lys Ala Ile Met Lys Ile Ala
165 170 175

9.WO3

```
Ile Val Trp Ala Ile Ser Ile Gly Val Ser Val Pro Ile Pro Val Ile
            180                 185                 190

Gly Leu Arg Asp Glu Glu Lys Val Phe Val Asn Asn Thr Thr Cys Val
        195                 200                 205

Leu Asn Asp Pro Asn Phe Val Leu Ile Gly Ser Phe Val Ala Phe Phe
    210                 215                 220

Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Cys Leu Thr Ile Tyr Val
225                 230                 235                 240

Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His Thr Glu Glu Pro
                245                 250                 255

Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys Arg Asn Thr Ala
            260                 265                 270

Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln Asn Ala Arg Arg
        275                 280                 285

Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met Gln Ala Ile Asn
    290                 295                 300

Asn Glu Arg Lys Ala Lys Lys Val Leu Gly Ile Val Phe Phe Val Phe
305                 310                 315                 320

Leu Ile Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Leu Ser Val Leu
                325                 330                 335

Cys Glu Lys Ser Cys Asn Gln Lys Leu Met Glu Lys Leu Leu Asn Val
            340                 345                 350

Phe Val Trp Ile Gly Tyr Val Cys Ser Gly Ile Asn Pro Leu Val Tyr
        355                 360                 365

Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser Asn Tyr Leu Arg
    370                 375                 380

Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg Gln Ile Pro Arg
385                 390                 395                 400

Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn Val Asn Ile Tyr
                405                 410                 415

Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser Asp Asn Glu Pro
            420                 425                 430

Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro Val Asn Pro Ser
        435                 440                 445
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9.WO3

Ser Val Val Ser Glu Arg Ile Ser Ser Val
    450   455

<210> 28
<211> 1437
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 28
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ttaaatgatg acaacaggct ctacagtaat gactttaact ccggagaagc taacacttct 120

gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaagggtgc 180

ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactggtc tgctttactg 240

acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc 300

ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat 360

atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccatcctgta tgggtaccgg 420

tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg 480

gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc 540

atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg 600

accatatcag taggtatatc catgccaata ccagtctttg ggctacagga cgattcgaag 660

gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt 720

gtgtcatttt tcattccctt aaccatcatg gtgatcacct actttctaac tatcaaggtt 780

ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt 840

ctggatttcc tgaagtgctg caagaggaat acggccgagg aagagaactc tgcaaaccct 900

aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg 960

caggctatca acaatgaaag aaaagcttcg aaggtactgg gcatcgtctt cttcctgttt 1020

gtggtgatgt ggtgcccttt cttcatcaca aacatcatgg ccgtcatctg caaagagtcc 1080

tgcaatgagg atgtcattgg ggccctgctc aatgtgtttg tttggatcgg ttatctctct 1140

tcagcagtca acccactagt ctatactctg ttcaacaaaa tttaccgaag ggcattctcc 1200

aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1260

gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1320

gaaccggtga tcgagaaagc cagtgacaat gagcccggta tagagatgca agttgagaat 1380

ttagagttac cagtaaatcc ctccagtgtg gttagcgaaa ggattagcag tgtgtga 1437

<210> 29
<211> 478
<212> PRT
<213> Artificial

<220>

9.WO3

<223> Novel Sequence

<400> 29

Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
1 5 10 15

Ser Leu Met Gln Leu Asn Asp Asp Asn Arg Leu Tyr Ser Asn Asp Phe
20 25 30

Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
35 40 45

Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
50 55 60

Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
65 70 75 80

Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
85 90 95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
100 105 110

Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
115 120 125

Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
130 135 140

Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
145 150 155 160

Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
165 170 175

Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
180 185 190

Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
195 200 205

Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
210 215 220

Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
225 230 235 240

Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Phe Leu
245 250 255

9.WO3

Thr Ile Lys Val Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His
260 265 270

Thr Glu Glu Pro Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys
275 280 285

Arg Asn Thr Ala Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln
290 295 300

Asn Ala Arg Arg Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met
305 310 315 320

Gln Ala Ile Asn Asn Glu Arg Lys Ala Ser Lys Val Leu Gly Ile Val
325 330 335

Phe Phe Leu Phe Val Val Met Trp Cys Pro Phe Phe Ile Thr Asn Ile
340 345 350

Met Ala Val Ile Cys Lys Glu Ser Cys Asn Glu Asp Val Ile Gly Ala
355 360 365

Leu Leu Asn Val Phe Val Trp Ile Gly Tyr Leu Ser Ser Ala Val Asn
370 375 380

Pro Leu Val Tyr Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser
385 390 395 400

Asn Tyr Leu Arg Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg
405 410 415

Gln Ile Pro Arg Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn
420 425 430

Val Asn Ile Tyr Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser
435 440 445

Asp Asn Glu Pro Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro
450 455 460

Val Asn Pro Ser Ser Val Val Ser Glu Arg Ile Ser Ser Val
465 470 475

<210> 30
<211> 1437
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

<400> 30
atggatattc tttgtgaaga aaatacttct ttgagctcaa ctacgaactc cctaatgcaa 60

ttaaatgatg acaacaggct ctacagtaat gactttaact ccaagaagc taacacttct 120

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gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaagggtgc    180
ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactggtc tgctttactg    240
acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc    300
ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat    360
atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccatcctgta tgggtaccgg    420
tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg    480
gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc    540
atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg    600
accatatcag taggtatatc catgccaata ccagtctttg ggctacagga cgattcgaag    660
gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt    720
gtgtcatttt tcattcccct gacgattatg gtgattacgt attgcctgac catctacgtt    780
ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt    840
ctggatttcc tgaagtgctg caagaggaat acggccgagg aagagaactc tgcaaacccct    900
aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg    960
caggctatca acaatgaaag aaaagctaag aaagtccttg ggattgtttt ctttgtgttt   1020
ctgatcatgt ggtgcccttt cttcatcaca aacatcatgg ccgtcatctg caaagagtcc   1080
tgcaatgagg atgtcattgg ggccctgctc aatgtgtttg tttggatcgg ttatctctct   1140
tcagcagtca acccactagt ctatactctg ttcaacaaaa tttaccgaag ggcattctcc   1200
aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga   1260
gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat   1320
gaaccggtga tcgagaaagc cagtgacaat gagcccggta tagagatgca agttgagaat   1380
ttagagttac cagtaaatcc ctccagtgtg gttagcgaaa ggattagcag tgtgtga      1437
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<210>  31
<211>  478
<212>  PRT
<213>  Artificial

<220>
<223>  Novel Sequence

<400>  31

Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
1               5                   10                  15

Ser Leu Met Gln Leu Asn Asp Asp Asn Arg Leu Tyr Ser Asn Asp Phe
            20                  25                  30

Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
        35                  40                  45
```

9.WO3

```
Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
    50                  55                  60

Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
65                  70                  75                  80

Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
                85                  90                  95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
            100                 105                 110

Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
        115                 120                 125

Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
    130                 135                 140

Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
145                 150                 155                 160

Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
                165                 170                 175

Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
            180                 185                 190

Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
        195                 200                 205

Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
    210                 215                 220

Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
225                 230                 235                 240

Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Cys Leu
                245                 250                 255

Thr Ile Tyr Val Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His
            260                 265                 270

Thr Glu Glu Pro Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys
        275                 280                 285

Arg Asn Thr Ala Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln
    290                 295                 300

Asn Ala Arg Arg Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met
305                 310                 315                 320
```

9.WO3

```
Gln Ala Ile Asn Asn Glu Arg Lys Ala Lys Lys Val Leu Gly Ile Val
                325                 330                 335

Phe Phe Val Phe Leu Ile Met Trp Cys Pro Phe Phe Ile Thr Asn Ile
            340                 345                 350

Met Ala Val Ile Cys Lys Glu Ser Cys Asn Glu Asp Val Ile Gly Ala
        355                 360                 365

Leu Leu Asn Val Phe Val Trp Ile Gly Tyr Leu Ser Ser Ala Val Asn
    370                 375                 380

Pro Leu Val Tyr Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser
385                 390                 395                 400

Asn Tyr Leu Arg Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg
                405                 410                 415

Gln Ile Pro Arg Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn
            420                 425                 430

Val Asn Ile Tyr Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser
        435                 440                 445

Asp Asn Glu Pro Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro
    450                 455                 460

Val Asn Pro Ser Ser Val Val Ser Glu Arg Ile Ser Ser Val
465                 470                 475
```